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Vaccine technology transfer in a global health crisis: Actors, capabilities, and institutions

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ABSTRACT

The COVID-19 pandemic, which featured international pharmaceutical firms seeking to build global manufacturing networks to scale-up the supply of vaccines, has generated heightened interest in understanding the role of firm-to-firm technology transfer. While considerable attention has been given to tracking the extent of international vaccine technology transfer, we know little about how partnerships were established and work in practice. Understanding the challenges that such projects face, and how such challenges may be overcome, is crucially important. This paper provides an account of the partnership between the British-Swedish multinational pharmaceutical company AstraZeneca, the vaccine developer that has engaged in the most technology transfer and built the widest global manufacturing network, and Bio-Manguinhos, a public laboratory linked to Brazil's Ministry of Health. The case study demonstrates the importance of capabilities and regulatory flexibility. Moreover, the analysis highlights the role of political factors that affect the process of technology transfer, and innovation more broadly. Because of the risks involved and the need to quickly mobilize existing capabilities and build new ones, as well as the imperatives of coordinating among manufacturing and regulatory processes and allocating resources to make such arrangements feasible, technology transfer projects need to be enabled politically. Looking forward, the case study has implications for initiatives to expand technology transfer for broadened production of vaccines in the Global South.

1. Introduction

The COVID-19 pandemic generated heightened interest in understanding the role of international technology transfer as a means to increase the global production of vaccines. In building manufacturing networks to respond to unprecedented demands for vaccines, developers have transferred technology to partners around the globe. While the extent of technology transfer partnerships between COVID-19 vaccine developers in the Global North and local pharmaceutical companies in the Global South has been the subject of considerable debate, lauded by some for its extent and criticized by others for its limits (Maxmen, 2021, Cheng and Hinnant, 2021, McMahon, 2021, Schultz, 2021, Yamey et al., 2022, Jensen et al., 2022), the reliance on this approach to scaling-up production is unquestionably a defining feature of the pandemic (Bown and Bollyky, 2022, Fu et al., 2022, Maxmen, 2021, Krishtel and Hassan, 2021, McMahon, 2021, Mermelstein and Stevens, 2022, Schultz, 2021, Yamey et al., 2022, Santiago, 2020, O'Sullivan et al., 2020, World Health Organization, 2021b).

For all of the attention given to tracking and debating the extent of international vaccine technology transfer, we know little about what has happened – how partnerships were established and how they work in practice. COVID-19 presents new and different sets of challenges, due to the technological complexities of most of the new vaccines being used, the urgency of acting quickly, and difficulties created by the pandemic itself. With technology transfer for local production widely regarded by scholars, activists, and international organizations as essential for

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addressing COVID-19 and future global health crises (Yamey et al., 2022; Fu et al., 2022; Krishtel and Hassan, 2021; Bollyky et al., 2022), understanding the challenges that such projects face, and how such challenges may be overcome, is crucially important.

This paper provides an account of the partnership between the British-Swedish multinational pharmaceutical company AstraZeneca (AZ), the vaccine developer that has engaged in the most extensive technology transfer and built the broadest global manufacturing network,[2] and Bio-Manguinhos (BioM), a public laboratory linked to Brazil's Ministry of Health (MoH). As of late 2021, roughly 50 % of the COVID-19 vaccines used in Brazil came from the AZ-BioM partnership,[3] demonstrating the key role that technology transfer for local production can play in pandemic response.

Politics, capabilities, and regulatory flexibility proved critical in this case. BioM utilized an existing framework that permits public institutions to procure technological development contracts, and mobilized political support for urgent action in the context of a health emergency. BioM's previous experience of vaccine production and its skilled personnel were important too, providing essential building blocks for BioM's participation in this venture. And Brazil's health regulatory agency, which worked closely with AZ and BioM, nimbly adapting its procedures to support the project, proved fundamental throughout the entire process.

An important contribution of this analysis is highlighting the role of political factors that affect the process of technology transfer, and innovation more broadly (Chataway et al., 2010; Ramani and Urias, 2018; Uyarra et al., 2020; Chataway et al., 2007). Because of the risks involved and the need to quickly mobilize existing capabilities and build new ones, as well as the imperatives of coordinating among manufacturing and regulatory processes and allocating resources to make such arrangements feasible, technology transfer projects need to be enabled politically. In short, not only are local technological capabilities and supportive regulatory environments essential, but also the conditions to mobilize support within and outside of government institutions.

These dimensions of technology transfer can be better understood by studying the experiences of specific cases (Agarwal et al., 2007; Levin, 1987; Flynn, 2015). To be sure, AZ-BioM is not Brazil's only COVID-19 technology transfer partnership. The Butantan Institute, a laboratory of the state of São Paulo, partnered with the Chinese laboratory Sinovac Biotech, while 2 private firms, Eurofarma and União Química, entered into technology transfer collaborations for the BioNTech-Pfizer and Sputnik-V vaccines, respectively. Of these, the AZ-BioM partnership stands out for being the earliest ("at-risk," beginning while the vaccine was still in clinical trials), involving the greatest amount of technology transfer for the core elements of vaccine manufacturing, and having the most projected output.

In the next section, we present core issues related to technology transfer, particularly in relation to vaccines, and we discuss how the COVID-19 pandemic exacerbated traditional challenges and created new ones. To set the Brazilian context, the third section provides a brief account of Brazil's policies to encourage local vaccine production, and BioM's central role in these initiatives. We then present the case study, in Section 4 explaining how the partnership materialized; and in Section 5 examining the politics of its launch in Brazil, the capability-enhancement dimensions, and the facilitating role played by Brazil's health regulatory agency. The discussion and conclusion in the sixth section synthesize the main findings and point to their broader implications for technology transfer policy, and also discusses avenues for future research.

2. Challenges and opportunities for technology transfer in the COVID-19 pandemic

The COVID-19 pandemic has generated renewed attention to the role of technology transfer as an instrument for promoting access to essential biomedical products in global public health crises. Twenty years ago, the AIDS crisis brought discussions over access to essential medicines to the forefront of the global development agenda. New international rules on intellectual property (IP) had recently been introduced, requiring the extension of patents to pharmaceutical products, generating concerns about how patents and other forms of IP would affect global access to essential medicines – for AIDS and other diseases as well (T' Hoen et al., 2011, Lanjouw, 2003). The COVID-19 pandemic renewed these concerns and many of the debates regarding access to medical technologies, but with different challenges and opportunities.

An important characteristic of the COVID-19 pandemic is that a focal point of innovation efforts, and thus the subsequent discussions around technology transfer, have revolved around vaccines, which became available comparatively early in the health crisis.[4] Because vaccines are biological – rather than synthetic chemical – products that are harder to imitate at scale, and because of the absence of regulatory pathways for the approval of "generic" vaccines, independent production by non-originators is more difficult than is the case with most therapeutics (Gong et al., 2011; Price et al., 2020; Crager, 2014; United Nations Industrial Development Organization, 2017; Milstien et al., 2007; Milstien and Kaddar, 2010).[5] To be sure, with sufficient effort non-originator pharmaceutical firms could develop imitation versions of vaccines, but only at considerable expense and on time-scales that, in the context of a pandemic, might defeat the purpose of doing so.

These differences have important implications for the relationship between IP and global production. Where production depends on the active engagement of the originator, to help master production processes and satisfy regulatory requirements, the absence or removal of IP is unlikely to increase global supply. What is needed is not subtractive, i.e. removing IP, but rather additive, i.e. technology transfer from the originator to partners. In contrast, then, to what was witnessed with AIDS, where generic producers (public and private) could make abundant and affordable treatments available (Waning et al., 2010; Cassier and Correa, 2003), efforts to expand global supply of vaccines during the COVID-19 pandemic have depended on originator firms transferring technology and know-how to manufacturing partners (Bown and Bollyky, 2022, Fu et al., 2022, Maxmen, 2021, Krishtel and Hassan, 2021, McMahon, 2021, Mermelstein and Stevens, 2022, Schultz, 2021, Yamey et al., 2022, Santiago, 2020, O'Sullivan et al., 2020, World Health Organization, 2021b, Barnes-Weise et al., 2022).

Vaccine technology transfer from multinational pharmaceutical companies to laboratories in middle-income countries long pre-dates the COVID-19 pandemic, and previous studies have identified key barriers that need to be surmounted for this to succeed. These include lack of financial resources and difficulties in hiring appropriate personnel that

[2] The science data analytics company Airfinity records drug substance output of the AstraZeneca vaccine from producers in 12 locations across the globe, including Asia and Latin America. No other COVID-19 vaccine has more than 3 locations producing the drug substance, i.e. the core element of the vaccine, and for most vaccines production is based almost entirely in Europe and the USA. For similar observations, see Bown and Bollyky (2022) and the Vaccine Manufacturing page on Duke University's "Launch & Scale Speedometer (https://launchandscalefaster.org/covid-19/vaccinemanufacturing)

[3] Vaccination data can be accessed on the Ministry of Health website: https://infoms.saude.gov.br/extensions/DEMAS_C19_Vacina_v2/DEMAS_C19_Vacina_v2.html (accessed November 1, 2022).

[4] Sampat and Shadlen (2021) discuss innovation efforts toward COVID-19 vaccines and therapeutics. Glassman et al. (2022) compare the timing of vaccine availability relative to disease outbreak across a range of pathogens.

[5] Although the first part of this sentence is partially attenuated in the case of mRNA vaccines, which share some production characteristics with chemical-based drugs, they remain regulated as biologic products.

are needed for vaccine production (United Nations Industrial Development Organization, 2021, Ponce-De-leon et al., 2011, Beurret et al., 2012, Friede et al., 2011), missing appropriate physical infrastructure (Grohmann et al., 2016), and lack of investment in research and development capacity and inabilities to acquire specific equipment (Fox, 2017). More often than not, it is the production process, skilled workforce, and expertise in specific technological platforms that create the most important barriers (Zhan and Spennemann, 2020; Agarwal et al., 2007; United Nations Industrial Development Organization, 2021). Research has also pointed to the importance of regulators being engaged throughout the process (in the early stages to monitor the steps and consult as issues arise, and later in the process to conduct batch trials to assure consistency) (United Nations Industrial Development Organization, 2021). While these contributions have helped us understand vaccine technology transfer, our study provides a more dynamic view of the economic, political, and technological challenges, and the responses that they elicited.

Technology transfer during the COVID-19 pandemic presented new challenges to what were already complicated processes. Many of the vaccines for COVID-19 rely on new genetic, recombinant technology platforms that had limited (if any) previous use in humans (Pizza et al., 2021; Kyriakidis et al., 2021), and for which manufacturing strategies needed to be built essentially from scratch (Bown and Bollyky, 2022). To satisfy the massive and urgent demand created by the pandemic, several developers established global networks of suppliers and producers, requiring the transfer of technology and manufacturing know-how to new partners.[6] Often this commenced before the conclusion of clinical trials and proceeded on accelerated timelines, with work stages that in non-pandemic situations are typically sequential (e.g. process development, technology transfer, validation, regulatory activities) conducted in simultaneous fashion so that production could be ready once the vaccines were approved for use. As a further complication, in some instances technology transfer to manufacturing partners occurred while originators were still exploring the best ways to mass-produce the vaccines.

Rapid technology transfer throughout global production networks in the conext of a pandemic put new pressures on quality control, always a critical component of vaccine production, with each step of the production line needing to be consistent with predefined processes. All of the facilities involved need to be inspected, the inputs being used need to be monitored and approved by regulators, and all equipment, input and processes documented as meeting the necessary standards. Quality assurance teams from the vaccine developers must take the lead, ensuring that manufacturing and control steps are executed properly (Hatchett et al., 2021). Of course, such oversight and monitoring was problematic because of traveling restrictions during the pandemic. National regulatory authorities from countries involved throughout the supply networks, in addition to sharing information, are responsible for assuring Good Manufacturing Practices (among others) and auditing manufacturing facilities. This too becomes more difficult in the case of large supply chains that were quickly assembled in pandemic conditions.

Vaccine supply chains also underwent severe disruptions in 2021, due to enormous demand for inputs and export restrictions that some countries imposed (World Health Organization, 2021b; Hatchett et al., 2021). Many key inputs, including bioreactor bags, filters, and glass vials, are produced by a limited number of suppliers. Not only is it difficult for manufacturers to forecast demand for inputs, but the ensuing challenges to procurement – common throughout manufacturing – are accentuated in the pharmaceutical industry, where inputs are highly regulated and changes of suppliers need to be authorized by the supervising regulatory authorities.

In the specific case of AstraZeneca, the vaccine with the largest manufacturing network and that is the subject of this article, this of course originated at Oxford University. Once Oxford's team demonstrated that the vaccine could be manufactured at industrial scale, its production was licensed to the Serum Institute of India. Then, developing a "franchise" model of technology transfer featuring "distributed manufacturing," Oxford turned to AstraZeneca to build parallel, regional supply chains on 5 continents (UK Research and Innovation, 2021; Joe et al., 2022; Whipple, 2021; Garrison, 2020; Gilbert and Green, 2021). One of these was the agreement with BioM, for the Brazlian market.[7]

3. Contextualizing COVID-19 technology transfer in Brazil

Brazil's response to the COVID-19 pandemic was characterized by former President Jair Bolsonaro's (2019-2022) anti-science approach, including his consistent downplaying of the health threats posed by SARS-CoV-2, his refusal to follow the WHO guidelines on non-pharmaceutical interventions (Fonseca et al., 2021a), and his attempts to discredit vaccination (Muggah, 2021). Yet, notwithstanding these attributes and actions of the President, the federal government quickly adopted technology transfer for local production as its main strategy to access COVID-19 vaccines, and to that end allocated resources to find an appropriate partner and support the agreement with AZ, early in the pandemic. This decision was built on an existing strategy to orient national innovation and industrial policies toward satisfying the health needs of the nation. Indeed, reducing external vulnerability and stabilizing the supply of essential medicines via local production has a long history in Brazil, and COVID-19 would not be an exception (Flynn, 2008; Defendi and Santiago, 2021; Shadlen and Fonseca, 2013).

Other vaccine initiatives included participation in the pooled procurement scheme of the WHO, the COVAX Facility, which allowed upper-middle-income countries like Brazil to make advance purchases of small volumes of vaccines at a time when it was unclear which would be approved (Berkley, 2020). Yet COVAX was considered a back-up to local production, which it was expected would allow the country access to a larger number of doses, and at lower prices (Fonseca et al., 2021b). As witnessed in other countries, Brazil's MoH also engaged in purchasing doses directly from international pharmaceutical firms, such as Pfizer and Johnson & Johnson (J&J), steps that occurred in 2021, after these vaccines received regulatory authorization in Brazil.

As in other many other low- and middle-income countries, Brazil is also host to projects for the development of indigenous vaccines. However, a number of conditions of Brazil's vaccine innovation infrastructure that generate substantial obstacles for these projects, including low levels of funding, the lack of specialized immunobiological centers and manufacturing units, and limited experience producing a complete vaccine from initial laboratory studies to large-scale production (Zaparolli, 2021). Although this approach has yielded candidates in various stages of investigation it is far from the primary response to the pandemic.[8]

To understand BioM's role in the technology transfer from AZ, we need to take a step back and consider its emergence and growth as a vaccine producer. The emergence of Brazil's internationally recognized National Immunization Programme (NIP) in 1973 was fundamental to the creation and strengthening of BioM as a site for vaccine

[6] Druedahl et al. (2021) found that vaccine partnerships have featured transfer of materials (e.g., technical infrastructure) more than active knowledge transfer and collaborative learning.

[7] AZ established a separate technology transfer arrangement with partners in Argentina and Mexico to supply the rest of Latin America and the Caribbean. For analysis of this partnership, see Shadlen (2023, forthcoming).

[8] Of 16 indiengous COVID-19 vaccine projects, as of January 2023 two received authorization to conduct human clinical trials. "Estudos clínicos com vacinas," https://www.gov.br/anvisa/pt-br/assuntos/paf/coronavirus/vacinas/estudos-clinicos.

manufacturing (Homma et al., 2013). BioM is part of Fiocruz, Latin America's largest biomedical institution, and is affiliated with the MoH. BioM was established in 1976 in the context of a meningitis epidemic, the need to quickly vaccinate the population, and the Brazilian government's keen interest in expanding technological development. Since then BioM has engaged in multiple technology transfer agreements for local production of new vaccines (United Nations Industrial Development Organization, 2021). This approach allowed BioM to produce a range of vaccines using different technological approaches (e.g. egg-based and cell-based) and yielding a range of formulations, including trivalent and tetravalent doses to protect against multiple viruses. BioM is a world leader in Yellow Fever vaccine production, for example, which was prequalified by the WHO in 2001 thus allowing it to be supplied not only to the NIP but also to other countries (Xeyla, 2019). Indeed, Brazil emerged as an important player - together with Russia, China, and India - in improving global access to vaccines of public health importance (Kaddar et al., 2014; Milstien and Kaddar, 2010).

4. Prospecting and evaluation: the foundations of the AZ-BioM partnership

When the WHO declared COVID-19 a public health emergency of international concern in March 2020, a BioM team, working jointly with colleagues from the MoH, was already looking for vaccines that the institute could produce (Fialho et al., 2022). From the start, technology transfer that would allow for local production of the full vaccine was regarded as a key objective. Building upon – and expanding – an already-existing "prospecting" division, BioM set about evaluating candidates according to a range of criteria, including not just the state of development of the products and their appropriateness for Brazil's vaccination campaign, but also technological and manufacturing characteristics. Table 1 provides an overview of the main candidates that were identified and evaluated in the first half of 2020.

BioM officials regarded the vaccine emerging from the University of Oxford, in partnership with AZ, as particularly appropriate, as it was at an advanced stage of development, and the viral vector technology was complementary to the existing competencies of BioM in working with cells in bioreactors. Given its existing expertise, BioM expected that the manufacturing process would be fastest with this vaccine (Fundação Oswaldo Cruz, 2020b). BioM would be able to use existing facilities and build on its capabilities in biologics: fill-finish capacities used for Yellow Fever vaccines could be adjusted, and cell culture for production of the drug substance could be accomplished in a plant with bioreactors that was equipped to produce interferon but could be redeployed.[9] Also important was Oxford and AZ having announced their intent to build a global, distributed production network, which would feature transfer of technology to local partners for manufacture of the full vaccine – not just fill and finish but drug substance too, and not just in Europe and USA but also to partners in the Global South (Joe et al., 2022; Whipple, 2021; Garrison, 2020). Critically, AZ was not only aiming for full technology transfer, but also dedicating resources to help this to proceed quickly.

No other vaccine shared these characteristics. Sinovac's vaccine was inappropriate, as it uses inactivated virus particles that require biosafety level 3 manufacturing facilities. Although the J&J vaccine uses the same viral vector technology as Oxford/AZ, and BioM officials report that they had discussions about local production, this candidate was regarded as too risky; still being in earlier stages of development and less likely to be available quickly enough, and the extent of technology transfer available was uncertain.[10] Given that BioM had experience in technology transfer with J&J (including a project that was on-going as of early 2020), the lack of a partnership for this vaccine appears surprising. Yet BioM's experience with J&J is reflected in the company's approach to global production of COVID-19 vaccine production: in contrast to AZ, J&J has fewer partners, with less geographic scope (none in Latin America), and less technology transfer involved (mostly fill-finish).[11] Nor were partnerships for the mRNA vaccines feasible: despite these vaccines' attractiveness in terms of being highly adaptable and also being in advanced states of development, they would require building new infrastructure and developing new skills, both challenging propositions in the middle of a pandemic when speed was of the essence. Moreover, the developers of the leading candidates, such as BioNTech-Pfizer (working in collaboration) and Moderna, were at the time even less active in including producers in the Global South in their manufacturing networks (see footnote 1).[12]

The partnership with AZ, as announced in June 2020, would proceed in 2 stages (Rochabrun, 2020). In the initial stage, BioM would import the drug substance and complete the process of manufacturing the final drug product (fill-finish) at its facilities in Rio de Janeiro. In the second stage, BioM would learn to produce the drug substance locally too, and thus proceed to manufacture the full vaccine. An important feature of this partnership is that BioM's relationship with AZ was as a licensee, rather than contract manufacturer. Concretely, this meant that BioM was producing and selling the vaccine directly to the MoH, with payment of a royalty to AZ, in contrast to BioM producing for AZ to then sell to the MoH. To be sure, the differences in this sort of relationship are not to be exaggerated, as what BioM could do with its output was restricted by the terms of the license set by AZ (e.g. BioM can only sell to Brazil's MoH), and in the first stage the amount BioM could produce was constrained by how much drug substance AZ supplied, but this status was regarded as important by the actors involved.[13]

It is important to underscore the broader opportunities, beyond COVID-19 per se, that BioM targeted in partnering with AZ and learning to produce this vaccine. Accessing the adenovirus, viral-vector technology, it was expected, would position BioM on a new research and knowledge pathway. Although the immediate objective was to contribute to the COVID-19 pandemic response in Brazil with the local production of vaccines, the technology transfer promised by this partnership would grant BioM access to a new technological platform that could be applied to additional products – vaccines, gene therapies, and other biologics – going forward. The capability enhancement dimensions need to be stressed: technology transfer would not only enable a faster route to COVID-19 vaccine production in Brazil, but the acquisition of new competencies in a new technological area would also open new possibilities for BioM to collaborate with more external actors and participate in viral vector-based projects.[14] In fact, as a result of this experience BioM ended up merging its units for vaccines and

[9] The demand for interferon in Brazil diminished considerably with the arrival of new antivirals (Interview 7, August 18, 2022).

[10] Interview 8, August 18, 2022.

[11] Medeiros et al. (2022: 4755) report that AZ was "the only company willing to transfer the entire technology."

[12] Brazil's prospecting campaign did not end with the AZ agreement. In August 2020 the Ministry of the Economy unsuccessfully approached Pfizer about engaging in technology transfer (Irajá, 2021). In August 2021, Pfizer eventually announced an agreement with Eurofarma for local fill-finish of the mRNA COVID-19 vaccine. Pfizer also announced a similar arrangement for local fill-finish with Biovac in South Africa (Reuters, 2021; Burger and Mishra, 2021). Moderna, which reached arrangements with a regional distributor, plans to supply Latin America (including Brazil) via exports (https://www.pharmaceutical-technology.com/news/moderna-vaccine-agreement-adium/)

[13] BioM informants report that the terms of the license agreement call for any subsequent modifications to the vaccine (e.g., adjustment to variants, new formulations) made by AZ or BioM to be shared with the other partner. Interview 8, August 18, 2022.

[14] For all BioM's experience making vaccines, this would be its first against a respiratory virus (Caride et al., 2022). Although our informants did not express this explicitly as an opportunity, it seems reasonable to regard it as such: the science and skills promised by this collaboration would allow BioM to expand into the area of vaccines against respiratory viruses.

Table 1
BioM's prospecting and evaluation candidates.

COVID-19 vaccine developer	Platform	Development stage[a]	Technology readiness level[b]	Adequacy[c]	Existence of a licensed vaccine for human use using the same platform
Oxford/AstraZeneca	Nonreplicating viral vector	Phase II/III	TRL7	++++	No
CanSino Biological	Nonreplicating viral vector	Phase II	TRL 6/7	++++	Yes
Moderna	Nucleic acid (mRNA)	Phase II	TRL 6 /7	+++++	No
Johnson & Johnson	Nonreplicating viral vector	Pre-clinical	TRL 4/5	++++	No
Pfizer/BioNTech	Nucleic acid (mRNA)	Phase I/II	TRL 6/7	+++++	No
Sinovac Biotech	Inactivated virus	Phase I/II		++	Yes
Novavax	Protein sub-unit	Phase I/II		+++	Yes
Inovio Pharmaceuticals	Nucleic acid (DNA)	Phase I	TRL 5/6	++++	No
Clover Biopharmaceuticals	Protein sub-unit	Phase I	TRL 5/6	+++	Yes
University of Queensland	Protein sub-unit	Pre-clinical	TRL 4/5	+++	Yes
Gamaleya Research Institute of Epidemiology and Microbiology	Nonreplicating viral vector	Phase I	TRL 5/6	++++	No
Sinopharm	Inactivated virus	Phase I/II	TRL 6 /7	++	Yes
Bharat Biotech	Inactivated virus	Pre-clinical	TRL 4/5	++	Yes

Source: Adapted from Fialho et al. (2022).
[a] As of June 26, 2020 (date of the decision for the AstraZeneca partnership).
[b] Technology Readiness Level (TRL) is an index that evaluates the progress of early-stage technological projects, ranging from 1 (still in conceptualization stage) to 9 (demonstrated usefulness).
[c] Flexibility and versatility of the technological platform with regard to eventual adjustments to vaccine targets.

biosimilars, creating a new Department of Bio-Products.

To conclude this section it is worth underscoring that IP was not regarded by BioM as presenting obstacles to be removed. Although Oxford scientists had obtained patents on the adenovirus vaccine platform in many countries, there were no patents (granted or pending) in Brazil (Medeiros et al., 2022 p. 4756),[15] and in any case, as part of the technology transfer agreement, AZ committed to sharing its proprietary know-how and data voluntarily. The fact that BioM was not an independent producer, but rather working under the conditions set by AZ according to the terms of the licensee, did not constitute a drawback. To the contrary, as BioM officials knew that on their own they could not produce the vaccine fast enough or realize the array of capability enhancements, working closely with AZ as licensee was considered an attraction.[16]

5. Promoting the partnership: the role of actors, capabilities, and institutions

Once BioM and AZ agreed to collaborate, several steps and actions had to be taken to effectively promote the partnership. This section reflects on BioM/Fiocruz's actions to push the collaboration forward by negotiating the support of state and non-state actors, the capability gains and strategies to streamline technology transfer, and the pivotal role of regulatory flexibility. These crucial elements allowed the AZ-BioM partnership to succeed in the context of political and public health crises.

5.1. Activation: overcoming legal and political stumbling blocks

BioM's initial investments to prepare for producing the AZ vaccine were made prior to the product being authorized for use by Brazil's (or any country's) regulatory agency, while clinical trials were on-going and before the efficacy of the vaccine was known. To deploy public resources in this way, when there may never have been a useable vaccine to produce, required the MoH to utilize a special procurement contract. Specifically, *Encomenda tecnológica* (Portuguese acronym ETEC), which is part of the 2004 Innovation Law and the 2016 Science, Technology and Innovation Code, allows public institutions to enter into development contracts for technological products that require regulatory approval, even when such approval is still outstanding. ETEC relates to public procurement for innovation, a policy much applied in the European context as a measure to use government purchasing power to stimulate innovation (Edquist and Zabala-Iturriagagoitia, 2012). Bruno Portela, a legal consultant of the Ministry of Economy involved in drafting the agreement, attributes the MoH's ability to sign the most important contract for public procurement of scientific innovation in the history of the country to the existence of the ETEC option (Biomanguinhos, 2021).

While ETEC's existence as a legal instrument created an opportunity, there needed to be a consensus within and outside government to make the AZ-BioM partnership come to fruition. This is because the project was risky, potentially leaving officials involved vulnerable if things went wrong, and the use of ETEC, a highly complex legal instrument, could still be questioned in the courts. To ensure transparency and minimize the risk of legal challenges, the contract agreement was consulted by various actors, including the Attorney General's Office (Ministério Público) (Falcão and Vivas, 2020) and the Institute for Applied Economic Research, a public agency that provides technical assistance to the government on economic and social policies (Rauen, 2020).[17]

Fiocruz's technical and coordinating capacities proved fundamental

[15] VaxPal, a database of patent landscapes for COVID-19 vaccines, reports a single application in Brazil for the Oxford/AstraZeneca vaccine (BR112013030222), filed in 2012 and recorded as withdrawn (https://www.vaxpal.org/patent/?uuid=31e6fad1-e15f-468a-a313-cc5b3c3caf19 accessed Oct 6, 2022). Because VaxPal does not report the date of the withdrawal, we consulted the database of the Brazilian patent office (INPI) to investigate if BR112013030222 was still pending at the time that the AZ-BioM technology transfer agreement was being arranged. According to the INPI database (https://busca.inpi.gov.br/pePI/jsp/patentes/PatenteSearchBasico.jsp accessed Oct 6, 2022), in 2017, three years before the pandemic, the applicant stopped paying renewal fees to keep the application active and subject to examination.
[16] Interview 9, August 19, 2022.
[17] In 2021, the Federal Court of Accounts (TCU) awarded Fiocruz for its actions against the pandemic, including production of vaccines (Bergamo, 2021). Despite Congress investigation on corruption allegations in vaccine procurement, the BioM/AZ agreement were never questioned by any politicians, auditing institution, or the media regarding its procedures (Interview 13, September 26, 2022).

for creating consensus and releasing funding for the AZ-BioM project. Members of Congress from multiple parties visited BioM in July 2020 to learn more about the collaboration with AZ. Fiocruz officials expressed the need for funding to be able to conclude the technology transfer agreement, a decision that was pending the approval of the Ministry of Economy. When returning to Brasilia, members of Congress negotiated with the Ministry of Economy to allocate funds for the technology transfer (Agência Câmara de Notícias, 2020). In addition, constant interactions with technical teams from within the MoH, featuring Fiocruz provision of risk analyses of the project and documentation of BioM's adequate production capacities, were crucial in securing the MoH's and the Ministry of Economy's support and getting the agreement off the ground. And Fiocruz's long-established reputation within civil society and its quick and robust response to the emerging pandemic, e.g. by providing COVID-19 tests and technical assistance for public laboratories throughout the country to manufacture tests, suggested that it – specifically, BioM, its laboratory for biologic products – was well-positioned to lead the national production of COVID-19 vaccines through a technology transfer agreement of the sort proposed. As one Fiocruz informant noted:

> "Our efforts have been very technical not only in relation to the vaccines, but also to tests etc. We are talking about 121 years of [Fiocruz's] history […] it is not easy to do things in Brazil, but we already have tradition and commitment […] Fiocruz's response to pandemics such as that of smallpox, bubonic plague and yellow fever [meant] that society is aware that the best way to fight this pandemic is through scientific knowledge, and this is what legitimized all the projects developed by Fiocruz".[18]

The AZ-BioM project gained political momentum when the governor of São Paulo, Joao Doria, a political rival of the president, announced a partnership with Sinovac in June 2020. This triggered what local media called 'the war of vaccines' (Cancian, 2020), with Bolsonaro and São Paulo's governor competing to bring the first Covid-19 shots into the country. The president mocked Sinovac's vaccine: "We [the federal government] joined that consortium there in Oxford. It is not from that other country [China], okay, guys? It is from Oxford over there [in the UK]" (BBC Monitoring Americas, 2020).

In August 2020, President Bolsonaro issued a provisional measure that guaranteed a USD 97 million investment in the AZ-BioM technology transfer (*Medida Provisória* 994/2020).[19] That the Bolsonaro government would take such a proactive step was anything but natural, given the President's broader approach to the COVID-19 pandemic and vaccines. Competition with the government of São Paulo made the federal government interested in promoting the AZ-BioM agreement, converting pressure from Congress and Fiocruz's active engagement with key stakeholders into a political opportunity.

Fiocruz generated backing for the AZ–BioM partnership, not just within government (Congress and the Executive), but outside government as well. Philanthropists and private sector actors got on board too: Jorge Paulo Lemann's Foundation sponsored AZ's clinical trials in Brazil (Fundação Lemann, 2020); Itau Bank and Ambev/Inbev, Brazil's largest banking company and brewing company, respectively, donated USD 20 million to Fiocruz for the adaptation of its manufacturing facilities (Fundação Oswaldo Cruz, 2020a). In addition, these companies provided assistance with logistics, particularly important for this project, which required rapid procurement of equipment, management of a number of new inputs, and quick distribution across the country.[20]

5.2. Expanding capabilities: technology transfer and local production

The AZ-BioM partnership proceeded from the downstream to the upstream stages of the production process, as is common with vaccine technology transfer (United Nations Industrial Development Organization, 2017). In the first stage, AZ committed to supplying the drug substance to BioM, which would undertake the fill-finish steps to complete the manufacturing process for an initial 30 million doses. Pending completion of clinical trials and regulatory approval of the vaccine, another 70 million doses would be produced this way.[21] The second stage involved the internalization of the full production process, enabling BioM to manufacture the drug substance, and thus the entire vaccine. Both stages were accompanied by the transfer of technology, know-how, and key materials.

The capability gains from the initial stage of technology transfer included improvements to quality control processes and fill–finish operations. As an experienced vaccine manufacturer, BioM already had advanced capabilities in key areas, including documentation, analytics, and quality control requirements, and special-purpose "clean rooms" that satisfy temperature and sterility standards. BioM worked with AZ to conform with the new standards that would be required and, importantly, to master the specific steps for the particular viral vector vaccine. Technology transfer for fill-finish involved transferring expertise in unfreezing the imported drug substances, formulation, and sterile injection of precise volumes into vials. All of this needed to be accomplished rapidly and with capacities to operate at high volumes, as part of pandemic response, and under strict quality control. Indeed, expertise to improve quality management at the recipient site forms an essential part of the technology transfer process. BioM raced to complete these steps and ready itself for undertaking the final steps in vaccine production. As one informant put it, "we should be waiting for the *IFA*, the *IFA* shouldn't be waiting for us."[22]

The core technological advancements came in the second stage, with BioM learning to manufacture the drug substance. The AZ vaccine uses a non-replicating viral vector, a modified version of a different virus (in this case, a chimpanzee adenovirus that causes colds or flu-like symptoms, but modified so as to not replicate inside human cells), to deliver the genetic code of the SARS-CoV-2 spike-protein, which generates an immune response (Center for Disease Control, 2021). Although BioM possessed the technology for cell culture in bioreactors and protein purification (indeed, it otherwise would not have been regarded as a prospective partner by AZ), it needed to learn how to apply its existing capabilities to viral vector production. As virtually all BioM informants expressed it, this technology transfer partnership featured BioM learning a new approach based on molecular biology, something that was more complex than previous BioM projects.

The key to the second stage was transfer of the cell lines, virus seed, and culture medium from AZ. To achieve the same clinical results, BioM (and all the producers in AZ's global production network) would need to use the same starting materials and proceed following the same steps (Joe et al., 2022).[23] To prepare, staff received training to defrost different biobanks, as the cell lines were received at a temperature of −150 °C. BioM received two capsules to train with. Just as BioM readied its equipment and processes to be "waiting for the IFA" in the first stage, BioM made sure to be prepared for receipt of the key starting materials from AZ for the second stage.

In June 2021, after the contract for the second stage of the technology transfer was signed, BioM received the cell lines from AZ. From

[18] Interview 6, July 27, 2021.

[19] This expenditure is in addition to the funds committed to purchasing the first doses from BioM.

[20] Interview 7 and 8, August 18, 2022.

[21] The MoH committed USD 317 million to purchase 100.4 million doses from BioM (Fundação Oswaldo Cruz, 2020c).

[22] IFA is Portuguese for "active pharmaceutical ingredient," which is how the drug substance is referred to in Brazil. Interview 5, July 22, 2021.

[23] Otherwise BioM would be regarded as producing a different product and therefore need to conduct its own clinical trials.

that point BioM estimated a period of three months to achieve the first batch of the COVID-19 vaccine, produced fully in Brazil (Lisboa, 2021). Normally, internalization of technology could have taken up to 10 years to complete, though in this instance adaptation of the manufacturing facility was initiated in parallel to the first stage of technology transfer, and subsequent steps were treated with urgency. In January 2022, BioM received regulatory approval of its locally produced drug substance (Agencia Fiocruz, 2022), and the first 550,000 doses – of an expected 45 million doses ordered by the MoH – were delivered in February 2022 (Fundação Oswaldo Cruz, 2022).

5.3. Regulatory flexibility: the role of ANVISA

Effective regulation can improve the quality of locally manufactured products and facilitate entry into international markets (Twesigye et al., 2021). However, low- and middle-income countries vary in their capacity to regulate vaccines, not just because authorities are often under-resourced and lacking legal mandates, but also due to their unfamiliarity with regulating novel technologies.

Brazil's health regulatory agency, ANVISA, played a crucial role throughout the technology transfer process. ANVISA is responsible for clinical trials, product approvals, and post-marketing surveillance, as well as plant inspection. Part of numerous international drug and vaccine harmonization forums, ANVISA is regarded as among the most stringent health regulatory agencies and a reference agency in Latin America (Pan American Health Organization, 2021).

ANVISA's role in the COVID vaccine project included adjustment of the agency's operating procedures to make officials available on short notice for unscheduled meetings with BioM, thus enabling constant communication to resolve technical issues, as well as on-sight inspections.[24] Previously, ANVISA would only initiate a regulatory review after all stages of clinical trials and documents were completed. In this case, rolling submission allowed AZ and BioM to submit documentation as clinical trials results were being released. Similar processes had already been adopted in mature regulatory agencies such as the US Food and Drug Administration and European Medicine Agency. According to BioM informants, this was crucial to expedite the approval process: "ANVISA could have said [document] accepted or not accepted, but instead the agency helped building up the [streamlined production] process. They were part of the process, not a passive agent."[25] Overall, ANVISA issued 53 new resolutions that made regulations during the pandemic more flexible. These included regulations not only for vaccines, but also for diagnostic kits and medicines. "Anvisa understood [the urgency of the context], and acted in advance."[26]

The first stage of the technology transfer also involved on-sight inspections by ANVISA of WuXi Biologics, the Chinese firm that, on behalf of AZ, was supplying the drug substance to BioM for fill-finish. The inspections aimed to assess whether the Chinese laboratory met the necessary conditions for ANVISA to issue a Good Manufacturing Practice (GMP) certification (Guimarães et al., 2022).

More broadly, ANVISA's agility helped keep Brazil's vaccination program on track when the AZ-BioM partnership was experiencing hiccups in its early stages. Although a delivery of 100 million doses from BioM to the MoH was projected as part of the first stage of the local production project, BioM encountered important complications during the manufacturing process, due to delayed delivery of key inputs and technical problems with some machines, creating a shortfall. In response, and to be able to commence vaccination in January 2021, the MoH imported 4 million doses of the vaccine from India, where it was produced by another AZ partner, the Serum Institute. However, as this version of the vaccine was not originally intended to be used in Brazil, ANVISA needed to issue a separate emergency use authorization. This process was accomplished following two weeks of constant communications between ANVISA and AstraZeneca.[27]

Finally, for the second stage of technology transfer, the drug substance production, in April 2021 ANVISA inspected all alterations made by BioM to its facilities, to then issue the GMP certificate. This allowed BioM to receive the cell bank and virus seeds, the starting materials needed to make the vaccine, initially test batches for inspection of the manufacturing process, then for validation, and finally, once approved, batches that could be delivered to the MoH (Barbosa et al., 2022). In January 2022, ANVISA approved the request to include BioM as a drug substance producer of the AstraZeneca vaccine by assessing the equivalence of the production process and ensuring that the doses produced in Brazil went through the same stages of manufacturing and used equivalent analytical methods as the original AZ product (Agencia Fiocruz, 2022). This decision allowed BioM to finally produce the first 100 % Brazilian-developed vaccine.

In sum, the role of ANVISA, which did not just accelerate and facilitate the manufacturing process by adapting its processes and issuing quick guidance concerning manufacturing and clinical trials, but also ensured that unforeseen challenges were promptly addressed and resolved, illustrates the importance of close dialogue and collaboration between regulators and drug producers.

6. Discussion and conclusion

In this study we identified the challenges that COVID-19 vaccine technology transfer to a manufacturer in the Global South needed to overcome, and the steps that the local partner in Brazil took – alone, jointly with the originator, and in collaboration with other actors in the Brazilian state. The analysis allows us to understand the success of the AZ-BioM partnership, which generated a major source of vaccines for the MoH. Our analysis focuses on three vectors of factors, related to political action, capabilities, and regulation.

Mobilizing existing capabilities in the context of ambiguity and emergency was crucial for overcoming both traditional and pandemic-specific challenges to technology transfer. Legal tools, such as the ETEC, highly skilled personnel, and ANVISA's agility were indispensable, but on their own these factors were unlikely to secure a successful outcome. BioM's ability to mobilize support, within and outside government institutions, proved critical for the technology transfer project and the timely delivery of COVID-19 vaccines.

The political elements of technology transfer merit further emphasis. Broad support for technology transfer within and outside government does not come automatically, as the value of local production is not universally recognized and corruption in public procurement is widely feared. Yet Fiocruz was able to build on its reputation for responding to public health emergencies and its experience working with a wide range of different actors to build this support – even bringing on board a sceptical President who otherwise demonstrated extreme reluctance to take measures against the pandemic.

The political lessons are relevant for the effective promotion of technology transfer from originator firms in the Global North to recipient firms in the Global South, a topic of interest beyond the COVID-19 pandemic per se. In 2021, the WHO's World Health Assembly adopted a resolution on "Strengthening local production of medicines and other health technologies to improve access," which identifies a number of actions to foster the technological development of and equitable access to life-saving biomedicals (World Health Organization, 2021a). Although the actions suggested may appear as straightforward technical steps, they are political in nature as they affect actors differently and generate conflicting interests. Integrating political economy analysis into innovation policies can help decision-makers develop more

[24] Interview 4, July 22, 2021.
[25] Interview 4, July 22, 2021.
[26] Idem.
[27] Interview 4, July 22, 2021.

effective approaches to navigate the challenges of technology transfer.

Although our study is primarily focused on implications for technology transfer policy in the context of global health crises, our analysis resonates with previous work on innovation as well. Yaqub and Nightingale (2012) analysis of poliomyelitis vaccine development, for example, suggests project outcomes can depend as much on the governance of the innovation ecosystem as the complexity of the technology. Similarly, other authors have pointed to the roles of "hub" organizations (Chataway et al., 2007; Chataway et al., 2010) and "institutional entrepreneurs" (Uyarra et al., 2020). Our findings regarding the agency of BioM (and Fiocruz) are consistent with this body of scholarship.

We have also emphasized the motivations and capabilities of the parties involved in the technology transfer, both establishing the partnership and allowing it to succeed. Obviously, the presence of an originator with the desire and means to share its technology, know-how, and data is indispensable. This was in short supply during the pandemic; AZ appears unique in this regard. Yet that commitment was only the starting point. To establish a global manufacturing network, AZ had to figure out what capabilities it was lacking internally, find appropriate global partners to fill these gaps, and then dedicate resources (legal and technical) to advance the collaborations as quickly as possible. That BioM could participate in AZ's network is of course a reflection of its own capabilities built over previous decades: with a different historical trajectory, BioM would never have been a useful partner for AZ in the first place.

Once the partnership began, the local actor's pre-existing capabilities proved even more important. Unable to proceed according to established technology transfer protocols during the pandemic, BioM and AZ needed to improvise. Due to travel constraints, for example, technology transfer meetings mostly occurred via online video conferences. This adapted form of training and knowledge transfer relied on expertise that BioM had gained from previous technology transfer projects. "We invented thousands of ways of training [including] taking pictures of the dish, and asking them if [what we were doing] was correct, sending them our test results, videos etc."[28] Or consider that AZ's production plans anticipated the use of 400-l single-use bioreactor bags, which BioM was unable to secure due to supply chain disruptions. Coordinating with AZ and ANVISA, BioM instead used available 300-l production tanks, repurposing these from their intended use in another project.[29] BioM was able to streamline technology transfer under such unfavorable conditions thanks to the technological, manufacturing and management capabalities developed over the previous decades. Just as not all originators shared AZ's disposition to technology transfer, not all potential partners exhibited BioM's attributes.

To be sure, the fortuitous presence of both a committed technology-sender and capable technology-recipient able to work flexibly is not always observed. Yet BioM is not unique; AZ established similar partnerships across the globe. Thus, probing deeply to understand how this specific partnership was established and functioned, though making the research more granular, provides important general lessons for technology transfer in pandemic conditions. Indeed, our hope is that the findings in this paper will inspire subsequent case studies that explore the dynamics of international technology transfer for the production of medical countermeasures.

Attention should also be given to thinking about how to encourage originator companies to transfer technology more widely. Though analyzing different approaches to technology transfer and global production is beyond the scope of this article, understanding why AZ pursued one path and Pfizer another, for example, is essential. Likewise, more consideration of how the array of innovation incentives can be used to encourage technology transfer, and why firms are likely to respond differently to similar incentives, are imperative.

Lastly, the findings in this paper have broader implications for technology transfer in the context of public health emergencies, where not only are local skills and capabilities essential, but also the conditions to mobilize them. Initiatives to expand local production capabilities, such as the WHO-led hubs in South Africa and Latin America for mRNA vaccines, require stable funding and strong regulatory oversight. Although the characteristics of mRNA create specific opportunities and challenges that distinguish those technology transfer projects, there are important commonalities too, in that factors that allow partnerships to materialize and flourish need to be in place too.

CRediT authorship contribution statement

EMF and KCS contributed equally to this work: Conceptualization, Investigation, Data Curation, Methodology, Writing- Original draft, Writing - Review & Editing.

HMA: Investigation, Data Curation, Writing- Original draft, Writing - Review & Editing.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

The data that has been used is confidential.

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Appendix A. Interviews

Interview	Description	Place	Date
1	Local vaccine producer	Video conference	June 29, 2021
2	Local vaccine producer	Video conference	July 1, 2021
3	Local vaccine producer	Video conference	July 12, 2021
4	Local vaccine producer	Video conference	July 22, 2021
5	Local vaccine producer	Video conference	July 22, 2021
6	Government official	Video conference	July 27, 2021

(*continued on next page*)

[28] Interview 4, July 22, 2021.

[29] Interview 5, July 22, 2021.From AZ's perspective, that they were engaging in similar technology transfer processes with partners at multiple sites across the globe made the challenges even more daunting. For a discussion, see Joe et al. (2022: 53–55).

(*continued*)

Interview	Description	Place	Date
7	Local vaccine producer	Rio de Janeiro	August 18, 2022
8	Local vaccine producer	Rio de Janeiro	August 18, 2022
9	Government official	Rio de Janeiro	August 19, 2022
10	Local vaccine producer	São Paulo	August 24, 2022
11	Local vaccine producer	São Paulo	August 24, 2022
12	Local vaccine producer	São Paulo	August 26, 2022
13	Government official	Video conference	September 26, 2022

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