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Vaccine innovation model: A technology transfer perspective in pandemic contexts

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ABSTRACT

This work identifies the innovations that made it possible for the Bio-Manguinhos/Fiocruz Immunobiological Technology Institute to engage in the entire production of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) in Brazil, just 1.8 years after the COVID-19 pandemic was declared. The results were summarized in a case-based innovation model composed of 11 workstreams, 32 stages, 22 gates, 11 innovations, and 38 events. In terms of research contributions, three were found: (i) the identification of firm and government-level innovations allowing the substantial reduction in the COVID-19 vaccine time-to-market in Brazil; (ii) the presentation of empirical evidence supporting the new Outbreak Paradigm for vaccine research, development, and production; and (iii) the proposition of a conceptual model for describing innovations through the vaccine value chain in pandemic contexts, particularly when technology transfer is involved.

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1. Introduction

Vaccines are likely the most effective approach to sustainably controlling the COVID-19 pandemic [1]. Given the far-reaching impact of COVID-19, the race for a candidate vaccine has taken on unprecedented urgency and commitment across the globe [2]. Nevertheless, vaccine research and development (R&D) is a high-risk, expensive process, which typically takes multiple candidates and many years to produce a licensed vaccine [3]. Because of the cost and high failure rates, developers mostly follow a linear sequence of steps, with multiple pauses for data analysis and manufacturing process checks, a pathway that dramatically changed in response to COVID-19 [4]. The need for a fast-track R&D process gave rise to a new *Outbreak Paradigm* [4], which rapidly spilled over to the vaccine value chain, making the lack of production capacity worldwide even more evident [5–7].

Global production capacity is critical to pursuing mass immunization, and technology transfer consists of an effective strategy for accelerating its upscaling [8]. This is particularly true in developing countries that produce vaccines but have not developed their COVID-19 vaccines in time [9]. Brazil fits this context, since most of the vaccines introduced in the country stem from technology transfer agreements [10]. However, in the technology transfers carried out in Brazil, many, if not all, had in common a licensed vaccine and a well-defined manufacturing process, which was not the case with COVID-19 vaccines [11].

The complexity of transferring a technology still under development and the speed imposed by the pandemic context require not only collaboration between technology partners, but also innovations that go beyond the transfer activities themselves. Moreover, making these innovations possible needs a cross-domain understanding of the vaccine value chain and the collaboration difficulties among the various stakeholders involved [12,13].

Over the years, substantial work in developing vaccine innovation models has been carried out. For instance, Hamidi et al. [9] proposed a technology transfer framework based on the Haemophilus Influenzae Type B project undertaken at Intravacc. Van de Burgwal et al. [13] integrated the complex array of steps required for vaccine R&D into an innovation cycle. O'Sullivan et al. [8] presented a technology transfer framework intended to shorten the COVID-19 time-to-market. Finally, Lurie et al. [4] deductively proposed a model for developing COVID-19 vaccines at pandemic speed.

Nevertheless, none of these models can fully describe innovations along the vaccine value chain in pandemic contexts,

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particularly when technology transfer is involved. The models considering technology transfer do so endogenously, thus not accounting for external innovations that also contribute to the transferring outcomes [e.g., 8,9]. In turn, the models with a holistic view of the vaccine value chain either do not consider technology transfer [e.g., 4], or do not deepen into specifics on the recipient side [e.g., 13]. Moreover, the models developed before the COVID-19 pandemic did not contemplate parallelizing some important activities, such as clinical trials [e.g., 9,13]. Finally, except for the model by Hamidi et al. [9], which was empirically grounded, the remaining ones were conceived based on experts' opinions or deduced by authors, which only allow analytical generalization.

Aiming to bridge these gaps, this work undertook single-case research to identify the innovations that made it possible for the Bio-Manguinhos/Fiocruz Immunobiological Technology Institute[1] to engage in the entire manufacture of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) in Brazil, 1.8 years after the COVID-19 pandemic was declared. The results were summarized in a case-based innovation model composed of 11 workstreams, 32 stages, 22 gates, 11 innovations, and 38 events. Concerning the research contributions, three were found. The first was identification of firm and government-level innovations allowing the substantial reduction in the COVID-19 vaccine time-to-market in Brazil. Secondly, empirical evidence was presented supporting the new *Outbreak Paradigm* for vaccine research, development, and production. Finally, a conceptual model was proposed for describing innovations through the vaccine value chain in pandemic contexts, particularly when technology transfer is involved.

The remainder of this paper is structured as follows: Section 2 summarizes the reference models basing this research; Section 3 outlines the methodological research procedures employed to build a case-based innovation model; Section 4 presents the innovation model; followed by Section 5, which critically analyzes its managerial and theoretical implications; and, finally, Section 6 states some closing remarks, the research limitations, and future considerations.

2. Reference innovation models

Three reference models were used as the conceptual foundations for analyzing and summarizing the innovations that enabled it to produce the ChAdOx1 nCov-19 vaccine in its entirety. The first was the Vaccine Innovation Model (VIC) by Van de Burgwal et al. [13], which combines the principle of stage-gates by Cooper [14] with the Valorization and Technology Transfer Cycle by Ribeiro et al. [15] to provide a cross-domain understanding of the vaccine innovation value chain.

The VIC is composed of 29 stages and 28 gates, distributed in ten different but integrated workstreams and comprehensibly depicted in a circular fashion. The stage-gates are classified as defined (D), undefined (U), and monitoring (M). The defined stage-gates occur in a relatively predictable order and timing. The occurrence and timing of undefined stage-gates are contingent upon a wide variety of factors, while the monitoring stage-gates occur continuously and iteratively. In an integrated R&D process, the defined, undefined, and monitoring stage-gates occur in parallel workstreams, with the outcomes of one workstream influencing the other, as shown in Fig. A1 (Appendix A).

The second model used was that proposed by Hamidi et al. [9], which presents the overall technology transfer approach followed for the Haemophilus Influenzae Type B (Hib) project at Intravacc. This model is organized sequentially, and its main phases include: (i) preparation; (ii) start-up; (iii) implementation; (iv) evaluation; and (v) troubleshooting. The activities comprising each phase are further detailed in Fig. A2 (Appendix A).

Finally, the third reference adopted in this study was the O'Sullivan et al. model [8], which defines the required steps for transferring COVID-19 vaccine technologies. As proposed by Hamidi et al. [9], the model is organized in a sequence of steps which include: (i) sourcing and opportunity; (ii) sourcing feasibility; (iii) planning; (iv) technical transfer; (v) variation pack; (vi) registration; (vii) launch; and (viii) project evaluation. Further details on activities comprising the model are given in Fig. A3 (Appendix A). All three models transcend the firm's boundaries by addressing industry and government issues.

3. Research design

This work aimed at identifying the innovations that enabled complete production of the ChAdOx1 nCov-19 vaccine in Brazil. Due to its empirical and investigative nature [16], this study followed the six-stage methodology for single-case research by Cauchick Miguel [17]. Fig. 1 summarizes the research workflow, which started by defining the research objective in Step 1.

In Step 2, the reference models presented in Section 2 were found through a systematic literature review, as reasoned by Ermel et al. [18]. These models served as the conceptual basis for analyzing and summarizing the innovations that emerged during the subsequent steps of this study. In Step 3, the context and the unit of analysis were defined. Regarding the context, the COVID-19 pandemic in Brazil was chosen for two reasons. First, because an unprecedented event in history, such as the COVID-19 pandemic, required changes in the traditional processes of R&D, production, and distribution of vaccines worldwide [4]. Second, because, besides being considered one of the epicenters of the COVID-19 pandemic [19], Brazil is the most prominent vaccine producer in Latin America [10]. Concerning the unit of analysis, the technology transfer of the Oxford/AstraZeneca vaccine (ChAdOx1 nCoV-19) to Bio-Manguinhos/Fiocruz was also selected for two reasons. First, because Bio-Manguinhos/Fiocruz is a government-owned entity that supplies most vaccines composing the Brazilian National Immunization Program [3]. Second, because the Oxford/AstraZeneca vaccine was the first COVID-19 vaccine entirely produced in Brazil [20].

Next, in Step 4, the means for data collection and analysis were defined. Regarding the former, a questionnaire with open-ended questions along with document gathering were used as instruments, as recommended by Forza [21]. Both instruments were tested in Step 5, and, after two refinement cycles, were considered validated. In Step 6, in addition to the two respondents who participated in the pilot testing (Step 5), 59 other individuals directly involved in the technology transfer of the Oxford/AstraZeneca vaccine were interviewed (44 from Bio-Manguinhos/Fiocruz, 4 from AstraZeneca, 2 from the Brazilian Ministry of Health, 2 from the Brazilian Ministry of the Economy, 2 from the Scientific and Technical Committee of COVID-19 Vaccine-Associated Initiatives (Fiocruz), 2 from the Pan America Health Organization, 1 from Oxford University, 1 from Bridge & Co., and 1 from São Paulo University). The interviews were conducted remotely for approximately one hour each, and were video recorded. In these, 17 relevant documents, including contracts, memos and project reports, were suggested for analysis. Besides these, another 104 documents were collected in Step 7, giving rise to a corpus of analysis composed of 121 documents and 61 interview responses.

In Step 8, the corpus was analyzed in-depth, as proposed by Bardin [22]. As a result, 32 stages, 22 gates, 30 innovations, and 38 events emerged from the content analysis. Then, following the

[1] The Bio-Manguinhos/Fiocruz is a government-owned vaccine producer in Brazil (https://www.bio.fiocruz.br/).

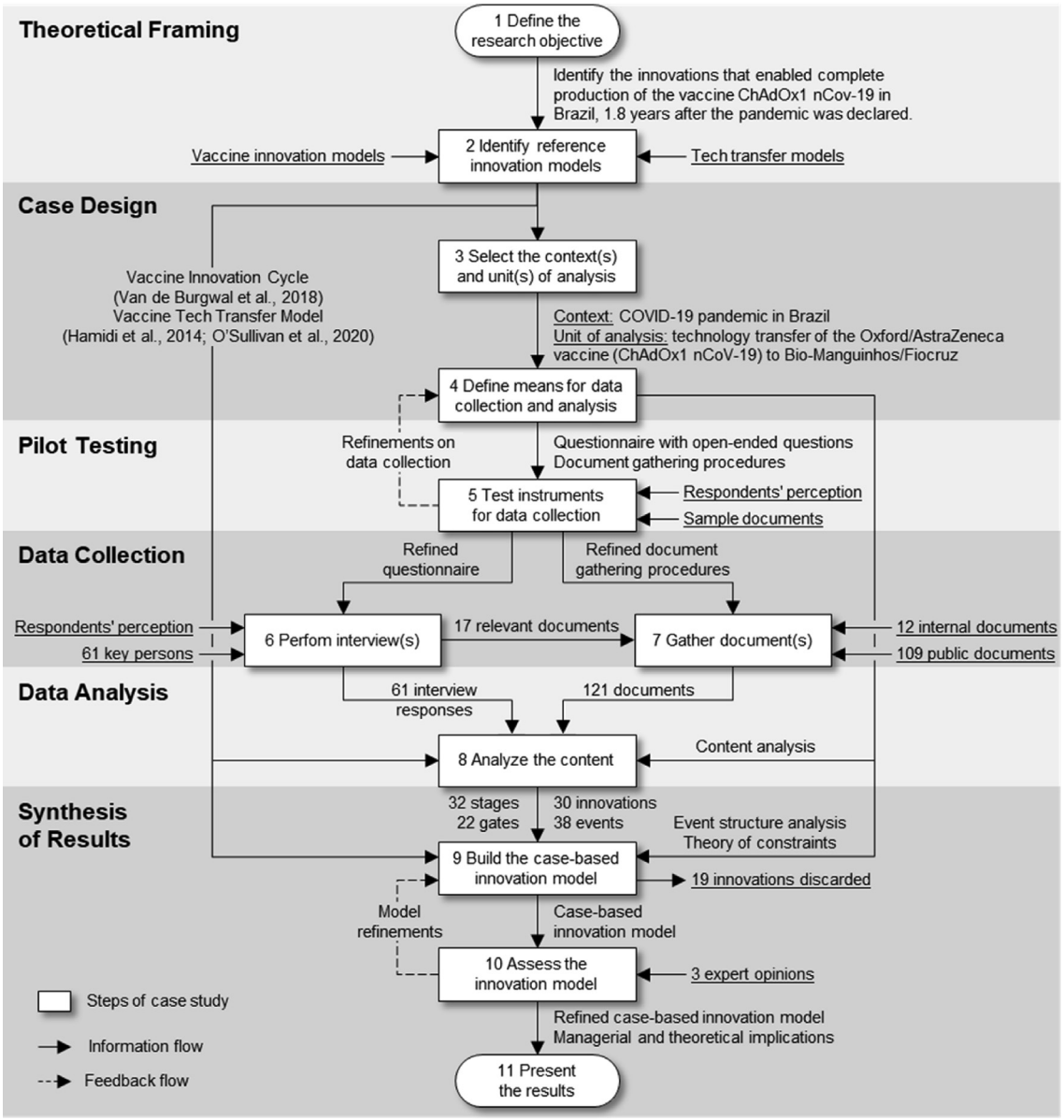

Fig. 1. Workflow adopted in conducting the single-case research.

counterfactual reasoning of Event Structure Analysis [23], combined with the sufficiency of cause principle retrieved from the Theory of Constraints [24], the case-based innovation model was built in Step 9. The building process started with selecting the stages, gates, innovations, and events that should compose the model. This selection was assisted by answering the following questions: (i) which stages and gates, if they had not occurred, would have made the R&D and production of the Oxford/AstraZeneca vaccine (ChAdOx1 nCoV-19) unfeasible in Brazil?; (ii) which innovations, had they not been implemented, would have made the R&D and production of the Oxford/AstraZeneca vaccine (ChAdOx1 nCoV-19) in Brazil unviable in 1.8 years after declaring the pandemic?; (iii) which events support the existence and temporal disposition of the stages, gates, and innovations found? As a result, 19 innovations were discarded (see Fig. 1), and the remaining elements were formally defined according to Tables 1 to 8. Next, the elements composing the innovation model were arranged based on the propositions of Van de Burgwal et al. [13], Hamidi et al. [9], and O'Sullivan et al. [8], as shown in Fig. 2. Although the original proposition of Van de Burgwal et al. [13] is depicted circularly, the case-based innovation model was presented linearly to highlight the time-lapse associated with its constituents. Then, in Step 10, the model's sufficiency and temporal disposition were assessed by three experts from Bio-Manguinhos/Fiocruz until it reached saturation, as proposed by Eisenhardt [25]. Finally, the results presented in the next section close Step 11 of this research.

4. Case-based innovation model

This section presents the case-based innovation model that explains, from the perspective of technology transfer in a pandemic context, how the Bio-Manguinhos/Fiocruz Immunobiological Technology Institute could enter full production of the first COVID-19 vaccine in Brazil, 1.8 years after the pandemic was declared. The innovation model organized in 11 workstreams and composed of 32 stages (S), 22 gates (D, U, or M), 11 innovations (I), and 38 events (E) is depicted in Fig. 2. Besides the graphical representation

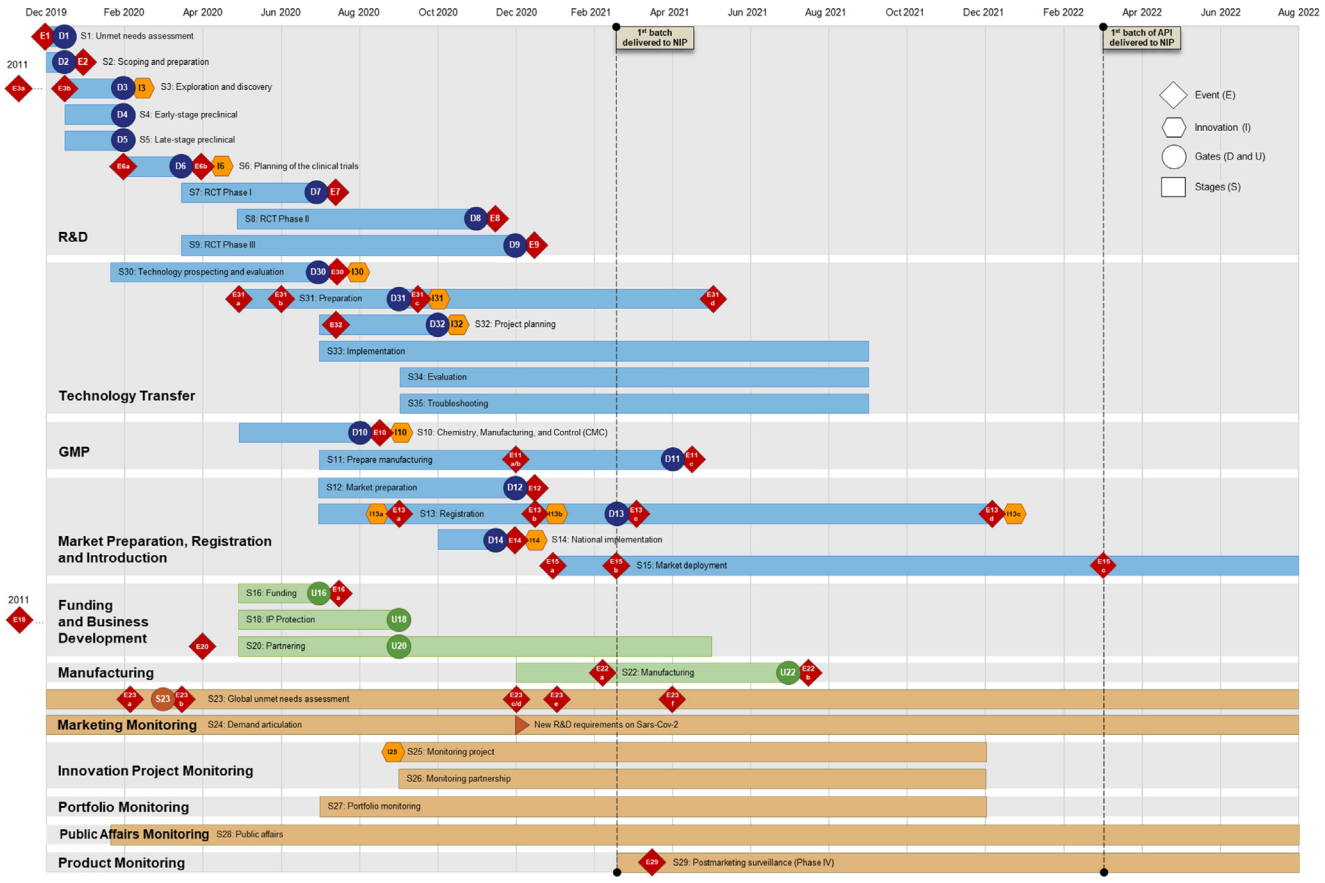

Fig. 2. Case-based innovation model.

of the model, the description of each workstream, along with its respective stages, gates, innovations, and events, is given throughout the following subsections.

4.1. Research and development (R&D)

This workstream refers to the R&D of the Oxford/AstraZeneca COVID-19 vaccine, named ChAdOx1 nCov-19, before registration. In January 2020, after the first cases of pneumonia with unknown causes reported at the end of 2019 in China (E1) [26], a team of researchers at Oxford University started developing a candidate vaccine (S1 and S2) against the supposed new coronavirus identified at the time (E2) [27]. About two months later, based on previous research by the Jenner Institute[2] on the adenovirus vector platform (ChAdOx1) [28] (E3a) and the genetic sequence of the novel virus (Sars-Cov-2) shared in January 2020 (E3b) [26], the preclinical development (S3, S4, and S5) of the candidate vaccine ChAdOx1 nCov-19 was concluded. This short lead time was possible given the high adaptability of the adenovirus vector platform to new targets as well as its safety profiles already demonstrated. Therefore, using the platform ChAdOx1 to develop the candidate vaccine ChAdOx1 nCov-19 was considered the first R&D innovation (I3).

Enabled by the Rolling Submission/Review - innovation I13a linked to the registration stage (S13) and presented in subsection 4.4, the adoption of adaptive clinical trials was identified as the second R&D innovation (I6). This is because it made it possible to run phases I, II, and III of clinical trials (S7, S8, and S9) in parallel. The first randomized controlled trial (Phase I/II) was conducted in the UK between April and May 2020 (E7) [29]. The second (Phase II/III) was also undertaken in the UK between May and August 2020 (E8) [30]. Finally, the third (Phase III) was conducted in the UK, Brazil, and South Africa between April and November 2020 (S9) [31]. Through the parallelization, it was possible to obtain data and share results on the safety, immunogenicity, and reactogenicity of the candidate vaccine ChAdOx1 nCov-19 in approximately nine months. When observed, in aggregate, the R&D stages were completed in about one year, a period appreciably shorter than the ten-year average typical of the traditional R&D paradigm [3,4,13,32,33]. Further details on the R&D workstream are given in Table 1.

4.2. Technology transfer

This workstream refers to the technology transfer of the ChAdOx1 nCov-19 vaccine to Bio-Manguinhos/Fiocruz. In February 2020, motivated by the spread of COVID-19 after the first cases reported in China (E1), the Institute started prospecting and evaluating technologies (S30) to fight the new virus. Right after, in March 2020, Bio-Manguinhos/Fiocruz created a technology prospecting network (TPN) dedicated to COVID-19. Developed from resources and processes of plant-based platforms, TPN started with a broader purpose that involved not only the transfer, but also the development of vaccine and biopharmaceutical technology. Nevertheless, given the complexity of developing a new medication in such a short time, Bio-Manguinhos/Fiocruz chose to focus its efforts on technology transfer issues. After six months of prospecting and articulation with the Brazilian Ministry of Health (BMH), by the end of July 2020, the TPN had identified and evaluated 278 candidate vaccines, of which 232 were in the

[2] The Jenner Institute is part of the Nuffield Department of medicine at Oxford University (https://www.jenner.ac.uk/).

Table 1
R&D elements composing the innovation model.

Stage	Gate	Event	Innovation
S1. Unmet needs assessment (Dec. 2019): Assessment of unmet needs to define R&D opportunities. Unmet needs may be medical, technical, or commercial in nature [13].	D1. Needs prioritization (Jan 2020): Selection and/or prioritization of R&D opportunities [13].	E1. (Dec. 2019) China reports to the World Health Organization (WHO) cases of pneumonia with unknown causes in Wuhan [26].	
S2. Scoping and preparation (Jan 2020): Scoping and preparation of projects to meet R&D opportunities [13].	D2. Start exploration (Jan. 2020): Allocation of resources for R&D projects based on technical, commercial, and budgetary criteria [13].	E2. (Jan. 2020) University of Oxford started developing the ChAdOx1 nCov-19 vaccine [27].	
S3. Exploration and discovery (Jan 2020): Elucidation of pathogenic mechanisms to identify targets and generate vaccine candidates [13].	D3. Lead identification (Feb. 2020): Identification of vaccine candidates for initial preclinical trials [13].	E3a. (May 2011) Development of a chimpanzee adenovirus vector with low human seroprevalence [28].E3b. (Jan. 2020) China publicly shared the genetic sequence of the virus Sars-Cov-2 [26].	I3. Use of adenovirus vector platform ChAdOx1 to develop the candidate vaccine ChAdOx1 nCov-19
S4. Early-stage preclinical (Jan 2020): Vaccine candidates are optimized and validated in simple animal models [13].	D4. Candidate nomination decision (Feb. 2020): Selection of candidate vaccines for final preclinical trials [13].		
S5. Late-stage preclinical (S5) (Jan. 2020): Vaccine candidates are tested in complex animal models to assess efficacy, immunogenicity, safety, and toxicity [13].	D5. Clinical trial planning begins (Feb. 2020): Selection of candidate vaccines for clinical trials [13].		
S6. Planning of the clinical trials (Feb 2020): Planning of the clinical trials and the regulatory strategy [13].	D6. First-in-man (Mar. 2020): Approval of regulatory authorities to start clinical trials [13].	E6a. (Feb. 2020) Jenner Institute at Oxford University signs a contract with Advent Srl to produce the first batch of ChAdOx1 nCov-19 vaccine for clinical trials [34].E6b. (Mar. 2020) Oxford University announces recruitment for clinical trials of ChAdOx1 nCov-19 vaccine [35].	I6. Adoption of adaptive clinical trials
S7. Randomized controlled trial (RCT) Phase I (Apr. 2020): Application of the candidate vaccine to a small number of volunteers to test safety and dose and to assess its initial ability to stimulate the immune system [13].	D7. Pre-Phase II (Jul. 2020): Based on technical, operational, and budgetary feasibility, the development proceeds to Phase II, the Phase I clinical trial is refined, or the development is terminated [13].	E7. (Jul. 2020) Publication of Phase I/II clinical trial results [29].	
S8. Randomized controlled trial (RCT) Phase II (May 2020): Application of the candidate vaccine in hundreds of volunteers to obtain more safety data, as well as to assess the vaccine's ability to stimulate the immune system (efficacy) [13].	D8. Pivotal development decision (Nov. 2020): Based on technical, budgetary, and regulatory feasibility, the development proceeds to Phase III, the Phase II clinical trial is refined, or the development is terminated [13].	E8. (Nov 2020) Publication of Phase II/II clinical trial results [30].	
S9. Randomized controlled trial (RCT) Phase III (Apr. 2020): Application of the vaccine candidate in thousands of volunteers to confirm its efficacy and learn more about adverse reactions in varied groups of individuals [13].	D9. Registration decision (Dec. 2020): Based on technical, commercial, and regulatory feasibility, the candidate vaccine moves to market preparation and registration steps, the Phase III clinical trial is refined, or development is terminated [13].	E9. (Dec. 2020) Publication of Phase III clinical trial results [31].	

Table 2
Technology transfer elements composing the innovation model.

Stage	Gate	Event	Innovation
S30. Technology prospecting and evaluation (Feb 2020): Prospection, evaluation, and selection of potential technologies to be transferred [8,9].	D30. Technology selection (July 2020): Selection of technologies and technology partners based on technical and economic criteria [9].	E30. (Jun. 2020) Issuance of a positive opinion by the Scientific and Technical Committee of COVID-19 Vaccine-Associated Initiatives (Fiocruz) on the technology prospecting study conducted by Bio-Manguinhos (event not disclosed at the time for strategic reasons).	30. Creation of a technological prospecting network (TPN) dedicated to COVID-19 issues.
S31. Preparation (May 2020): Exchange of information between technology owner and technology recipient on technical and economic issues involving the potential technology transfer contract [9].	D31. Technology transfer agreement (Sep 2020): Signing the technology transfer agreement [8,9].	E31a. (May 2020) Confidentiality agreement signed between Fiocruz and AstraZeneca (event not disclosed at the time for strategic reasons).E31b. (Jun. 2020) Statement in response to the letter from the British Ambassador to Brazil regarding the COVID-19 vaccine of Oxford/AstraZeneca [37]. E31c. (Sep. 2020) Signing of the Technological Order Agreement Term (TOAT) No. 01/2020 [11].E31d. (Jun 2021) Signing of the Technology Transfer Agreement [40].	I31. Use of the Technological Order Agreement Term (TOAT) as a legal instrument to transfer a technology still under development.
S32. Project planning (Aug. 2020): Preparation of the work breakdown structure and project schedule [9].	D32. Start implementation (Nov 2020): Allocation of resources for project implementation [8,9].	E32. (Aug. 2020) Contracting of an external consultancy for integrated project management [41].	I32. Establishment of a tailor-made structure and new management routines for the technology transfer project.
S33. Implementation (Jul. 2020): Transferring of technological knowledge to support decision-making [9].	This stage does not have a specific gate. Instead, it works as a support for stages S10, S11, and S22.		
S34. Evaluation (Sep 2020): Evaluation of the need for support, advice, training, and additional information [9].	This stage does not have a specific gate. Instead, it works as a support for stages S10, S11, and S22.		
S35. Troubleshooting (Sep 2020): Solving implementation-related issues [9].	This stage does not have a specific gate. Instead, it works as a support for stages S10, S11, and S22.		

Table 3
GMP elements composing the innovation model.

Stage	Gate	Event	Innovation
S10. Chemistry, manufacturing, and control (CMC) (May 2021): Evaluation of facilities and infrastructure required for production, specification of up/downstream processing platforms, and preparation of quality control tests in consultation with regulatory authorities [13].	D10. Specification of the manufacturing process (Aug. 2020): Specification and acquisition of equipment, inputs, and services for adequacy of the manufacturing process.	E10. (Aug. 2020) Acquisition of equipment, inputs, and services related to the API formulation process (event not disclosed at the time for strategic reasons).	I10. Use of a generic process of virus replication in cell culture to address the lack of information during the planning phase of API transfer.
S11. Prepare manufacturing (Sept. 2020): Adequacy of existing facilities and infrastructure, as well as ensuring the necessary resources for the entire operationalization of the vaccine production chain [13].	D11. Certification of technical operation conditions (Apr 2021): Certification of technical operation conditions of the industrial plant [13].	E11a. (Dec. 2020) ANVISA certifies technical operation conditions of AstraZeneca's (Wuxi Biologics) industrial plant where the imported API is produced [42].E11b. (Dec. 2020) Bio-Manguinhos/Fiocruz receives equipment and inputs for the formulation of API in Brazil (event not disclosed at the time for strategic reasons) .E11c. (Apr. 2021) ANVISA attests to technical operation conditions of the Bio-Manguinhos/Fiocruz industrial plant where the national API will be produced [43].	

Table 4
Elements of market preparation, registration and introduction composing the innovation model.

Stage	Gate	Event	Innovation
S12. Market preparation (Jul. 2020): Definition of market and pricing strategies [13].	D12. Launch decision point (Dec. 2020): Formalization and dissemination of the launch strategy (e.g., regions, price, dates, etc.), including a timeline for registration [13].	E12. (Dec. 2020) Bio-Manguinhos/Fiocruz releases Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) registration and production schedule [44].	
S13. Registration (Oct 2020): Preparation and submission of the Common Technical Document (CTD) to the regulatory authorities [13].	D13. Market authorization decision (Mar. 2021): Registration approval by regulatory authorities [13].	E13a. (Sep. 2020) Fiocruz submits the first package of documents to ANVISA for Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) registration [45].E13b. (Jan. 2021) ANVISA authorizes emergency use of Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) [52].E13c. (Mar. 2021) ANVISA grants Bio-Manguinhos/Fiocruz the first registration of a COVID-19 vaccine produced in Brazil [49].E13d. (Jan. 2022) Bio-Manguinhos/Fiocruz changes registration at ANVISA including national production of API [50].	I13a. Rolling submission/review (IN 77/2020; RDC 534/2021).I13b. Emergency use authorization (RDC 444/2020) .I13c. Post-registration petition (RDC 415/2020) .
S14. National implementation (Oct. 2020): Articulation of implementation strategy with government and stakeholders [13].	D14. Inclusion in immunization program (Dec 2020): Inclusion of the vaccine in the NIP [13].	E14. (Dec. 2020) Brazilian Ministry of Health presents the National Operationalization Plan for Vaccination against COVID-19, considering the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) [54].	I14. Inclusion of a vaccine without definitive registration in the NIP.
S15. Market deployment (Jan 2021): Use of the vaccine in the national immunization program [13].		E15a. (Jan. 2021) Bio-Manguinhos/Fiocruz releases to NIP two million doses of the Oxford/AstraZeneca vaccine imported from the Serum Institute, India, for emergency use [55].E15b. (Mar. 2021) Bio-Manguinhos/Fiocruz delivers to NIP the first batch of Oxford/AstraZeneca vaccine produced in Brazil with imported API [56].E15c. (Feb. 2022) Bio-Manguinhos/Fiocruz delivers to NIP the first batch of the Oxford/AstraZeneca vaccine with API produced in Brazil [57].	

Table 5
Elements of funding and business development composing the innovation model.

Stage	Gate	Event
S16. Funding (May 2020): Search and acquisition of funding to support development, production, or distribution stages [13].	U16. Formalization of funding (Aug. 2020): Release of funds for the execution of the development, production, or distribution stages [13].	E16. (Aug. 2020) Provisional Measure No. 994[58].
S18. Intellectual property protection (May 2020): Drafting, filing, and maintaining patent applications [13].	U18. Patents (Sept. 2020): Patent applications and decisions on maintaining patents in specific territories [13].	E18. (May 2011) Patent application for simian adenoviruses and hybrid adenoviral vectors [59].
S20. Partnering (May 2020): Identification and selection of partners to improve development, production, and distribution processes [13].	U20. Licensing (Sept. 2020): Signing of licensing agreement and/or a strategic partnership [13].	E20. (Apr. 2020) AstraZeneca and Oxford University announced an agreement to develop, produce, and distribute vaccine ChAdOx1 nCov-19 globally [60].

Table 6
Manufacturing elements composing the innovation model.

Stage	Gate	Event
S22. Manufacturing (Dec. 2020): Execution of up/downstream processes, quality assurance, quality control, and compilation of batch dossiers [13].	U22. Production upscaling (Sept. 2021): Start upscaling production upon validation of pilot batches in terms of consistency and stability [13].	E22a. (Mar. 2021) Bio-Manguinhos/Fiocruz starts upscaling production of COVID-19 vaccine with API imported from China [39].E22b. (Ago. 2021) Manguinhos/Fiocruz starts upscaling production of COVID-19 vaccine API formulated in Brazil [20].

Table 7
Market monitoring elements composing the innovation model.

Stage	Gate	Events
S23. Global unmet needs assessment (Dec. 2019): Assessment of unmet global needs from a social perspective [13].	U23. Global policy recommendations (Mar. 2020): Formulation of global policy recommendations, including vaccines of public health importance, target product profiles, and suggestions for funding [13].	E23a. (Mar. 2020) WHO declares the COVID-19 pandemic [26].E23b. (Mar. 2020) WHO releases a GRR against the new coronavirus [61]. E23c. (Dec. 2020) Alpha variant detected [62].E23d. (Dec. 2020) Beta variant detected [62].E23e. (Jan. 2021) Gamma variant detected [62].E23f. (Apr. 2021) Delta variant detected [62].
S24. Demand articulation (Dec. 2019): Prioritizing unmet needs, defining articulation factors, and reviewing global policy recommendations [13].	This stage does not have a specific gate. Instead, it works as a support for stage S23.	

Table 8
Innovation project monitoring elements composing the innovation model.

Stage	Gate	Innovation
S25. Project Monitoring (Sep. 2020): Monitoring of project performance evolution [13].	This stage does not have a specific gate. In general, several project controlling decisions are made at this stage.	I25. Establishment of a risk management routine
S26. Partnership monitoring (Sep. 2020): Monitoring the execution of contractual commitments between partners [13].	This stage does not have a specific gate. In general, several decisions concerning the partnership are made at this stage.	

exploratory or preclinical phases and 46 in the clinical phase [36]. In addition to the vaccines themselves, TPN identified up/downstream equipment required for their processing, which was particularly useful in the subsequent steps of technology transfer. Although the six months taken to prospect and evaluate emerging vaccine technologies was compatible with some traditional approaches [8], the amount of data gathered was large, and it would not be possible to process it without articulating the resources of the newly created TPN, which was considered the first innovation (I30) of this workstream.

In May 2020, based on the preliminary prospecting studies, Bio-Manguinhos/Fiocruz started negotiating with potential technology partners (S31). Of these, AstraZeneca[3] was the only company willing to transfer the entire technology. Moreover, it was the partner that had not only a vaccine platform in line with Bio-Manguinhos/Fiocruz capabilities, but also the one with the candidate vaccine in more advanced stages of clinical development at the time. The relationship between institutions began with the signing of a confidentiality agreement in May 2020 (E31a), and evolved with the BMH expressing interest in establishing a partnership to transfer the Oxford vaccine production technology to Brazil in June 2020 (E31b) [37]. In the same period, Bio-Manguinhos/Fiocruz concluded the study indicating that the technology of the Oxford vaccine (ChAdOx1 nCov-19) was the most suitable alternative from the technical and economic standpoints (S30) [36].

The formalization of the partnership between the institutions happened in two phases. The first, in September 2020, occurred through the Technological Order Agreement Term (TOAT) (E31c) [11], a legal instrument that allowed the acquisition of a technology still under development. This was the second innovation of this workstream (I31) since it was the only way for a government-owned institution in Brazil to fund a project of this nature and magnitude. The scope of the TOAT comprised the import of the active pharmaceutical ingredient (API) and the technology transfer for the vaccine's fill-finishing - formulation, filling, inspection, labeling, packaging, and quality control - in Brazil. Although the intentions were declared in the TOAT, the technology transfer for the API production was formalized in June 2021 through a Technology Transfer Agreement (E31d) [38].

Even before signing the TOAT, Bio-Manguinhos/Fiocruz began to articulate a new management and governance structure to handle the technology transfer project, which was considered the third innovation of this workstream (I32). Unlike the other projects conducted by the Institution, the complexity of transferring a technology under development, and the speed imposed by the pandemic context, required the creation of a tailor-made structure and new management routines for the project. The structure and routines were established based on six management pillars[4], and were supported by an external consultancy in integrated management (S32). Through both strategies, it was possible to plan (S32) and execute (S33) the technology transfer of the ChAdOx1 nCov-19 vaccine in eight months until the upscaling of fill-finishing (S22a) [39], and one year until the upscaling of API production (S22b) [20], processes that traditionally take between two and three years [9].

[3] The company holding the rights to develop, produce, and distribute the Oxford vaccine (ChAdOx1 nCov-19) worldwide [60].

[4] (i) Integrated management; (ii) technology partnering management; (iii) technology transfer management; (iv) infrastructure management; (v) regulatory compliance; and (vi) administrative management.

The implementation (S33) is a broad stage that often overlaps with the activities of others demanding technological knowledge in transfer to make their actions tangible (S10, S11, and S22). In other words, it is a supporting stage, which, together with the stages of evaluation (S34) and problem-solving (S35), were developed in parallel to the others to provide technological foundations for the decision-making. Table 2 provides further details on the technology transfer workstream.

4.3. Good manufacturing practices (GMP)

This workstream refers to good manufacturing practices (GMP). After defining the partner and the technology to be transferred (S30), Bio-Manguinhos/Fiocruz evaluated the facilities, infrastructure and equipment required for vaccine fill-finishing and API production (S10). To overcome the lack of information in the early stages of the project and mitigate the impact of this situation on the implementation schedule, a generic process of virus replication in cell culture was used as a reference for decision-making on API production. This innovation (I10), along with the expertise of AstraZeneca's suppliers (discovered by TPN), enabled the specification and acquisition of up/downstream equipment and supplies for API production by the end of August 2020 (E10).

Still in August 2020, in parallel to the specifications and acquisitions involving the API production, Bio-Manguinhos/Fiocruz began the preparation of fill-finishing (S11). This stage started with the operations of formulation, filling, inspection, labeling, packaging, and quality control, which, by the end of December 2020, were certified as to their technical operating conditions by the Brazilian Health Surveillance Agency (ANVISA) (E11a) [42]. In the same period, the equipment and supplies for API processing arrived (E11b). Four months later, in April 2021, ANVISA also granted the certification of technical operation conditions for API production (E11c) [43]. Details on the GMP workstream are given in Table 3.

4.4. Market preparation, registration and introduction

This workstream relates to the market preparation, registration and introduction of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) into Brazil. After selecting the partner and technology (S30), Bio-Manguinhos/Fiocruz began the market preparation (S12). At this stage, the supply and pricing strategies were defined, contemplating the delivery of 100.4 million doses of the vaccine to the Brazilian Unified Health System (SUS) by December 2021, at approximately 3.30 USD per dose. The formalization of these strategies occurred, first, by the signing of the TOAT (E31c) [11] in September 2020, and then by disclosing the vaccine registration and production schedules (E12) in December of the same year [44].

The registration stage (S13) took place in parallel. It started in September 2020 by submitting the first document package to ANVISA (E13a) [45]. This partial submission was only possible due to the Rolling Submission/Review [46], considered the first innovation of this stage (I13a). Unlike the traditional process and enabled by IN 77/2020 [47] and RDC 534/2021 [48], the Rolling Submission/Review allowed regulatory authorities to review the application documents in parallel with the clinical trials (S7, S8, and S9). This mechanism brought celerity to the process, enabling the ChAdOx1 nCov-19 vaccine with imported API to be licensed in Brazil six months after the first submission (E13c) [49], and 1.3 years when produced with national API (E13d) [50]. This represented a shorter duration than the two-year average of the traditional submission process [3,4,33]. With further regard to registration, the following innovations were also identified: the Emergency Use Authorization (EUA) (I13b) that, enabled by the RDC 444/2020 [51], permitted immunizing the population with vaccines without a definitive license, thus bringing forward the introduction of the ChAdOx1 nCov-19 vaccine in Brazil by approximately three months (E13b) [52]; and the Post-Registration Petition (I13c), which, through the RDC 415/2020 [53], granted the rapid change of the API manufacturing site for the ChAdOx1 nCov-19 vaccine license (E13d) [50].

After the market preparation (S12) and concurrently with the registration stage (S13), national implementation was carried out (S14). Through the articulation of Bio-Manguinhos/Fiocruz, the Brazilian Federal Government and other stakeholders, the ChAdOx1 nCov-19 vaccine was included in the National Immunization Plan (NIP) in December 2020 (S14) [54]. The inclusion of a vaccine without a definitive license in the NIP was considered the third innovation of this workstream (I14), since it enabled the immediate start of vaccination (S15) in two situations: first, after EUA (S13b); and second, after the issue of a definitive license (S13c). Regarding the first situation (E13b), in January 2021, Bio-Manguinhos/Fiocruz released to the NIP two million doses of the ChAdOx1 nCov-19 vaccine, imported from the Serum Institute, India (E15a) [55]. In the second (E13c), in March 2021, Bio-Manguinhos/Fiocruz delivered to NIP 4.2 million doses of the vaccine produced in Brazil with imported API (E15b) [56]. Finally, in February 2022, after delivering more than 180 million doses to the NIP, Bio-Manguinhos/Fiocruz delivered the first batches of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) produced entirely in Brazil (E15c) [57]. Table 4 provides further details on the market preparation, registration, and introduction of the COVID-19 vaccine in Brazil.

4.5. Funding and business development

This workstream refers to the funding and partnership development concerning the technology transfer of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) to Bio-Manguinhos/Fiocruz. Therefore, some stages not applicable to this case, such as scouting (S17), spin-off company (S19), and acquisition (S21), as well as their respective actors (Vaccitech, Oxford Sciences Innovation, etc.)[5], are not addressed in this subsection.

Regarding the funding stage (S16), in August 2020, through Provisional Measure No. 994 [58], the Brazilian Federal Government opened extraordinary credit of approximately R$ 2 billion to fund the technology transfer of the ChAdOx1 nCov-1 vaccine. Besides the transfer of unpatented technology (know-how) (S33), this process also included the licensing of patents in the country (S18). Nevertheless, despite the patent of the chimpanzee adenovirus platform (ChAdOx1) filed in the UK and the USA (E18) [59], there was no evidence, at least during the pandemic period, of a patent application related to the ChAdOx1 nCov-19 vaccine. This and other technical, economic and regulatory issues guided the negotiations between AstraZeneca and Bio-Manguinhos/Fiocruz (S20), which ended with the formalization of the partnership, as presented in subsection 4.2. It should also be noted that this partnership would not have been possible if the agreement between the Oxford University and AstraZeneca had not been signed in April 2020 (E20) [60]. Table 5 summarizes the workstream of funding and business development.

4.6. Manufacturing

Comprising a single stage (S22), this workstream refers to executing API production and fill-finishing of the ChAdOx1 nCov-19 vaccine at the Bio-Manguinhos/Fiocruz facilities. As well as the preparation stage (S11), manufacturing occurred in two phases.

[5] For further details on the stages and actors not considered in this subsection, see the works by Van de Burgwal et al. [13] and Garrison [71].

The first, in March 2021, involved the production of pre-validation and validated vaccine batches with the API imported from China (S22a) [39]. The second, in August 2021, involved the production of pre-validation and validated vaccine batches with the API produced in Brazil (E22b) [20]. In both phases, the consistency and stability tests reached the specified parameters; therefore, it was possible to upscale production. Table 6 presents the stage, gate and events related to manufacturing.

4.7. Market monitoring

This workstream relates to assessing and prioritizing unmet global needs concerning the COVID-19 pandemic (S23 and S24). Coordinated by the WHO, the monitoring initiatives started after the first cases of COVID-19 reported in the city of Wuhan, China, in December 2019 (E1). In March 2020, the WHO declared the COVID-19 as a pandemic (E23a) [26] and released a R&D Blueprint against the novel coronavirus (E23b) [61]. This R&D Blueprint had two objectives, one short-term and the other long-term. The first objective was to rapidly contain the spread of the new virus (Sars-Cov-2), while the second was to encourage preparedness against new pandemics.

Given the genetic mutability and transmissibility of the coronavirus, the direction of the R&D Blueprint has not remained static. This is because two new variants, Alpha (E23c) and Beta (E23d), were identified in December 2020, and another two, Gamma (E23e) and Delta (E24d), in January and April 2021, respectively [62]. The latter had a high transmission capacity and was responsible for new outbreaks worldwide. The emergence of these and other variants brought new demands for R&D, reinforcing the cyclical nature of the vaccine innovation model proposed by Van de Burgwal et al. [13]. Table 7 summarizes the market monitoring workstream.

4.8. Innovation project monitoring

This workstream relates to the project and technology partnership monitoring (S25 and S26), which were simultaneously carried out, from the definition of the technology and the partner (S30) up to the formal closure of the project in December 2021. Although the stages S25, S26, S27, S28, and S29 were presented independently, the monitoring activities occurred in an integrated fashion, as explained in subsection 4.2. In this context, besides synchronizing and transferring the project activities to the organizational routines, the major challenge was to mitigate the risks that could compromise the implementation deadline. Therefore, to anticipate discussions about potential threats and identify actions to counteract them, Bio-Manguinhos/Fiocruz established a risk monitoring routine, which made it possible to execute the technology transfer within the planned timeframe. This monitoring routine was also considered an innovation associated with monitoring activities (I25). Table 8 provides further details on the workstream of innovation project monitoring.

4.9. Monitoring of product, portfolio, and public affairs

Besides the project and technology partnership monitoring (S25 and S26), the technology transfer of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) required Bio-Manguinhos/Fiocruz to monitor the product (S29), portfolio (S27), and public affairs (S28). Regarding the product, in April 2021, the European Medical Agency (EMA) concluded that unusual blood clots with low blood platelets should be listed as extremely rare side effects associated with the vaccine (E29) [63].

In terms of the portfolio (S27), as of August 2020, Bio-Manguinhos/Fiocruz turned its attention to the products that could potentially be affected by the decision to internalize the API production and fill-filling of the ChAdOx1 nCov-19 vaccine. Considering the API production, three ongoing projects, Beta-INF, Golimumab and Erythropoietin, were postponed. Regarding final processing, the Yellow Fever and Triple-Viral vaccines, although affected, did not have their deliveries compromised with the NIP. Unfortunately, the same was not possible for the Infliximab, Inactivated Polio, and Pneumococcal vaccines, which had their delivery times compromised.

Finally, the monitoring and articulation of actions related to public affairs (S28) started at the beginning of the technological prospection and evaluation phase (S30). Bio-Manguinhos/Fiocruz is a government-owned entity; therefore, the decisions associated with combating the pandemic, more specifically those related to the vaccine, besides being audited by governmental agencies, also demanded their national disclosure.

5. Innovations and lessons

The innovations identified from the R&D of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) to its subsequent production in Brazil by Bio-Manguinhos/Fiocruz have brought lessons for the future. In managerial terms, the innovations substantially reduced the vaccine time-to-market. From the declaration of the COVID-19 pandemic to the release of the first batches of vaccines produced with the API imported from China, it took about 1.1 years. Considering vaccines produced with national API, it was approximately 1.8 years, notably shorter than the 12 years average traditionally taken [3,4,13,32,33]. These short time intervals by conventional standards, but still long for global public health emergencies, were crucial in immunizing the Brazilian population against COVID-19. Namely, of the individuals immunized with the first two doses up to December 2021, 35.1% were vaccinated with the Oxford/AstraZeneca vaccine [64].

From a theoretical perspective, the innovations provided empirical evidence for the new *Outbreak Paradigm* of vaccine R&D, as posed by Lurie et al. [4]. Furthermore, when viewed in aggregate, such as in the case-based model of Fig. 2, the innovations may explain the mechanisms making this new paradigm possible, even for non-pandemic contexts. Moreover, they highlight the influence of actions exogenous to technology transfer on its overall outcome, thus complementing previous endogenous-focused studies [8,9].

In total, 11 innovations were identified. They were summarized in Table 9 using the CIMO-logic by Denyer, Tranfield, and Van Aken [65]. CIMO-logic combines the principles of prescription and causality to explain the mechanisms (M), from which specific interventions (I) in problems-in-context (C) generate certain outcomes (O). The difference is that the interventions take the form of innovations in this work. In addition, following the taxonomy of Defendi, Madeira, and Borschiver [66] and Van de Burgwal et al. [13], innovations were also classified according to their type, extent, and workstream they belong.

Of the innovations found, two addressed the need to accelerate the R&D of COVID-19 vaccines (C1). The first (I3) consisted of using the adenovirus vector platform (ChAdOx1) to develop the candidate vaccine ChAdOx1 nCov-19 [28]. Technological in nature, this innovation allowed the rapid adaptation of a new vaccine platform to the genetic sequence of the virus Sars-Cov-2 (M3.1). Moreover, it enabled the use of the platform's safety profiles already demonstrated (M3.2), thus reducing the preclinical development lead time by approximately 4 years (O1.1) [33]. The second innovation (I6) was the adoption of adaptive clinical trials. This process innovation made it possible to run phases I, II, and III of clinical trials concurrently (M6), a different proposition if compared to the sequential pattern of the model by Van de Burgwal et al. [13]. This

Table 9
Summary of innovations identified in the technology transfer of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) to Bio-Manguinhos/Fiocruz.

(C)	Context	(I)	Innovation	Type	Extension	Workstream	(M)	Mechanism	(O)	Outcome
C1	Need to accelerate the R&D of COVID-19 vaccines.	I3	Use of adenovirus vector platform ChAdOx1 to develop the vaccine candidate ChAdOx1 nCov-19	Technological	Firm-level (Oxford Univ.)	R&D	M3.1	High capacity of the platform to adapt to new pathogenic mechanisms by replacing part of the genome of the viral vector by the gene of the target antigen	O1.1	Reduction in preclinical development lead time of approximately four years (S3, S4, and S5)
							M3.2	Previously demonstrated safety profiles		
		I6	Adoption of adaptive clinical trials	Process	Firm-level (Oxford Univ. and AstraZeneca	R&D	M6	Running the different phases of clinical trials in parallel by provisionally analyzing data and changing specifications during their conduct	O1.2	Reduction in clinical development lead time of approximately five years (S6, S7, S8, S9, and S10)
C2	Need to provide a COVID-19 vaccine to immunize the Brazilian population quickly	I30	Creation of a technology prospecting network (TPN) dedicated to COVID-19	Process	Firm-level (Bio/Fiocruz)	Tech transfer	M30	Network articulation of resources and processes of plant-based platforms	O2.1	Selection of technology and partner from the prospecting and evaluation of 278 candidate vaccines over six months
		I31	Use of the Technological Order Agreement Term (TOAT)	Process	Government-level (Br. Fed. Government)	Tech transfer	M31	Advance purchase commitment for the imported API and the transfer of formulation, filling, inspection, labeling, packaging, and quality control technology of the ChAdOx1 nCov-19 vaccine, conditional on achieving efficacy levels greater than 50% in the COVID-19 pandemic period	O2.2	It allowed a government-owned institution, such as Bio-Manguinhos/Fiocruz, to acquire technology under development
		I32	Establishment of a tailor-made structure and new management routines for the project	Process	Firm-level (Bio/Fiocruz)	Tech transfer	M32	Reducing project complexity by dividing the work into specialties	O2.3	Reduction in the technology transfer lead time by approximately one year, considering the production of the ChAdOx1 nCov-19 vaccine with national API and two years considering the production with imported API
		I25	Establishment of a risk management routine	Process	Firm-level (Bio/Fiocruz)	Innov. project monitoring	M25	Mitigation of risks that could compromise the vaccine availability in Brazil		
		I10	Use of a generic process of virus replication in cell culture	Process	Firm-level (Bio/Fiocruz)	GMP	M10	Specification and acquisition of equipment and supplies for API production in a context of low data available		
		I14	Inclusion of a vaccine without a definitive license in NIP	Process	Government-level (Br. Fed. Government)	Mkt. preparation, registration, and introduction	M14	Inclusion of the ChAdOx1 nCov-19 vaccine in the NIP in parallel with the registration process	O2.4	Enabled the immediate use of the ChAdOx1 nCov-19 vaccine at two points in time, after EUA and after definitive licensing
C3	Need for flexible regulatory pathways during the COVID-19 pandemic	I13a	Rolling submission/ review (IN 77/2020; RDC 534/2021)	Process	Government-level (ANVISA)	Mkt. preparation, registration, and introduction	M13a	Review of registration application documents in parallel with clinical trial execution	O3.1	Reduction in registration lead time of approximately 1.5 years
		I13b	Emergency use authorization (RDC 444/2020)	Process	Government-level (ANVISA)	Mkt. preparation, registration, and introduction	M13b	Authorization to immunize the Brazilian population with vaccines without a definitive license	O3.2	Anticipated by approximately three months the beginning of vaccination in Brazil
		I13c	Post-registration petition (RDC 415/2020)	Process	Government-level (ANVISA)	Mkt. preparation, registration, and introduction	M13c	Replacement of the API production site in the license of ChAdOx1 nCov-19 vaccine concurrently to the batch validation process	O3.3	Allowed the new license to be immediately effective as validated the batches

mechanism enabled a 5-year reduction in clinical development lead time (O1.2) [3,33]. Both innovations, I3 and I6, had a firm-level extension and were associated with two stakeholders of the technology transfer project, Oxford University and the biopharmaceutical AstraZeneca.

Six process innovations were instrumental in providing a COVID-19 vaccine to immunize the Brazilian population quickly (C2). The first (I30) consisted of creating a TPN dedicated to COVID-19 issues. By articulating networked resources and processes (M30), it was possible to evaluate data on 278 candidate vaccines in six months and select the technology that best fitted Brazilian needs and Bio-Manguinhos/Fiocruz capabilities (O2.1). Although the time employed in this process was compatible with the model by O'Sullivan et al. [8], the articulation of resources and processes in a network fashion was not pointed out by the authors as a mechanism to execute technology prospection. The second innovation (I31) referred to the use of TOAT as a mechanism for commitment to purchase in advance (M31). Used for the first time in Brazil, TOAT was the only legal instrument available for a government-owned institution to acquire technology under development (O2.2). The third innovation (I32) was creating a tailor-made structure and new management routines for the technology transfer project of the vaccine ChAdOx1 nCov-19. The organization of the project in pillars made it possible to divide its complexity and workload by thematic area (M32). This mechanism contributed to the planning and execution of the technology transfer in eight months until the upscaling of fill-finishing, and one year until the upscaling of API production (O2.3), processes that traditionally take between two and three years [9]. The following two innovations also influenced the outcome O2.3. The risk management routine (I25), which through anticipating discussions about potential threats and identifying actions to counteract them (M25), helped mitigate the risks that could compromise the vaccine time-to-market. Also, there was use of a generic process of virus replication in cell culture (I10) as a reference for specifying and acquiring up/downstream equipment and supplies for API production in a context of low data availability (M10). Finally, the sixth innovation associated with C2 was the inclusion of a vaccine without a definitive license in the NIP (I14). Adopted for the first time in Brazil, this activity being performed in parallel with the registration process (M14) enabled the immediate use of the ChAdOx1 nCov-19 vaccine, both after the EUA and after the definitive licensing (O2.4). The innovations I10, I25, I30, and I32, had a firm-level extension and were limited to Bio-Manguinhos/Fiocruz. In turn, the innovations I14 and I31 had a government-level extension and involved other instances of the Brazilian Federal Government, such as the Ministry of Health and the Ministry of Economics, to name a few.

Finally, three process innovations were imperative regarding the need for flexible regulatory pathways in the COVID-19 pandemic (C3). The first was the Rolling Submission/Review (IN 77/2020; RDC 534/2021) (I13a), which, unlike the traditional process, allowed ANVISA to review the application documents in parallel with the clinical trials (M13a). Influenced by other surveillance agencies (e.g., FDA, EMA, NMPA, etc.), this mechanism brought celerity to the process, enabling the ChAdOx1 nCov-19 vaccine to be licensed in Brazil six months after the first submission (O3.1). Considering the vaccine produced with the national API, the license was granted 1.3 years after the first submission, a short duration when compared to the two-year average typical of the traditional submission process [3,33]. The second innovation consisted of the EUA (RDC 444/2020) (I13b), which by immunizing the Brazilian population with a vaccine without a definitive license (M13b), brought forward the COVID-19 vaccination campaign by three months (O3.2). Finally, the third innovation refers to the Post-Registration Petition (RDC 415/2020) (I13c). Through it, it was possible to submit the change of the API production site in the ChAdOx1 nCov-19 vaccine license concurrently with the batch validation process (M13c). This initiative allowed the new license to be immediately effective in validating the batches (O3.3). All three innovations (I13a, I13b, and I13c) had a government-level extension, which, although they involved different instances of the Brazilian Ministry of Health, were conducted by ANVISA.

Some challenges had to be overcome to make a COVID-19 vaccine quickly available to the Brazilian population (C2). The first was having to transfer a technology still under development. Unlike all other technology transfers executed by Bio-Manguinhos/Fiocruz, the ChAdOx1 nCov-19 vaccine, and consequently the ChAdOx1 platform, were in the clinical development phase when the project began (E31c). This situation, moderated by the fact that AstraZeneca's production has been executed almost entirely by contracted manufacturing organizations (CMO), has made it difficult to access detailed information about the production process in the early project stages. In this sense, the risk was not specifying the up/downstream equipment in time or correctly, which was surpassed by innovation I10 together with the help of the AstraZeneca equipment suppliers identified by TPN. The second was that even making the specifications on time, there was a global demand for equipment and supplies, which in some cases required the retrofitting and relocation of equipment from other immunizers to produce the COVID-19 vaccine. Finally, the most challenging obstacle was executing the technology transfer during a pandemic, as, just like any other organization [6], the employees at Bio-Manguinhos/Fiocruz were also exposed to the new virus and consequently got sick. In addition to a reformulation of management and governance actions, this situation required devising and executing a contingency plan, which later became a coexistence plan, to maintain the Institute's operations active and safe throughout the COVID-19 pandemic.

From the technical point of view, it should be noted that the challenges were not more significant because Bio-Manguinhos/Fiocruz has accumulated competencies throughout an extensive set of technology transfer projects. These projects bequeathed a competitive industrial park and technical knowledge for the teams involved. In this sense, in terms of national and global public health, it is necessary to identify, evaluate and develop technology transfer resources and capabilities in different regions and countries.

In scientific terms, this work fills the gap of lack of references on technological transfers in pandemic contexts. Technological transfer requires attention, since it can contribute to the global public health strategy. The decentralization of production can be an important strategy for reducing supply risks, expanding production capacity, and, consequently, reducing costs and maximizing vaccination coverage. Additionally, technology transfer can constitute a mechanism to accelerate the response to future pandemics, since it benefits from installed and developed resources and capacities.

Complementary to the R&D of new vaccines and production technologies, the capacity to transfer technology quickly and expand the use of the installed base must be considered in seeking improved global health. Other issues not covered in this paper need to be considered, such as national health, intellectual property rights, and geopolitics, to name a few. In the case of Bio-Manguinhos/Fiocruz, because it is a government-owned institution, the regulatory challenges are an additional factor that needs to be addressed for both technology transfer and production to occur.

6. Closing remarks

This work identified 11 firm and government-level innovations that enabled Bio-Manguinhos/Fiocruz to engage in the entire man-

ufacturing process of the Oxford/AstraZeneca vaccine (ChAdOx1 nCov-19) in Brazil, 1.8 years after the COVID-19 pandemic was declared. It is a short time-to-market by conventional standards, but still long for global public health emergencies. From the technology transfer perspective, among the factors that prevented this time from being even shorter, the following stand out: (i) the need for works to provide appropriate infrastructure and utilities; and (ii) competition for up/downstream equipment and production supplies on a global scale.

On the technology recipient side, these factors are not solved only by employing more resources per time unit. There are often technical, physical or political constraints that prevent allocating more resources to the same activity, thus leading the project to a minimum duration, but different from zero [68]. This increases the belief that what should be transferred in emergencies, such as the COVID-19 pandemic, is the vaccine production technology (e.g., ChAdOx1 nCov-19) and not its platform (e.g., ChAdOx1). The latter should already be in the recipient's domain and consequently transferred or developed in non-emergency periods, thus using the rationale of preparedness rather than reactive actions [69]. Besides the innovations mentioned (see Table 9), at the firm level, perhaps the rationale of preparedness is one of the main lessons acquired during the COVID-19 pandemic. The awareness of this rationale, while still in the pandemic, moved the Institute forward to the technological development of a second-generation mRNA platform for COVID-19 vaccines. Developed from studies of therapeutic vaccines against cancer, this initiative was shared with the WHO, which, in September 2021, ended up selecting Bio-Manguinhos/Fiocruz as the development and production hub of vaccines with mRNA technology in Latin America [70]. With this ongoing project, the mRNA platform will be added to the adenovirus one, giving the Institute the ability to respond even faster to new emergencies, either by developing proprietary vaccines or incorporating vaccines developed by third parties.

In managerial terms, the innovations identified in this work substantially reduced the vaccine time-to-market from 12 years on average to approximately 1.8 years [3,4,13,32,33]. From a theoretical perspective, the innovations provided empirical evidence for the new *Outbreak Paradigm* of vaccine R&D [4]. Furthermore, when aggregated in a conceptual model, the innovations could shed light on the path dependence and mechanisms making this new paradigm possible. Moreover, they highlighted the influence of actions exogenous to technology transfer on its overall outcome [8,9]. However, despite the contributions described above, the study has some limitations. One is that the extension of the proposed innovation model is from firm to government level, leaving out important global level issues, such as the role of technology transfer in the decentralization of global vaccine production. The other is that, given the limited space that this type of publication allows, it was not possible to detail the technical and scientific challenges faced during the technology transfer of the vaccine ChAdOx1 nCov-19 to Bio-Manguinhos/Fiocruz, leaving them for future publications. Finally, this is a single case study related to the adenovirus platform. However, more have come into existence in the COVID-19 pandemic, related to other platforms. In this regard, a meta-synthesis of multiple primary studies evaluating the innovations that made it possible to rapidly advance research, development, production, and distribution of COVID-19 vaccines on a global scale would be welcome.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A

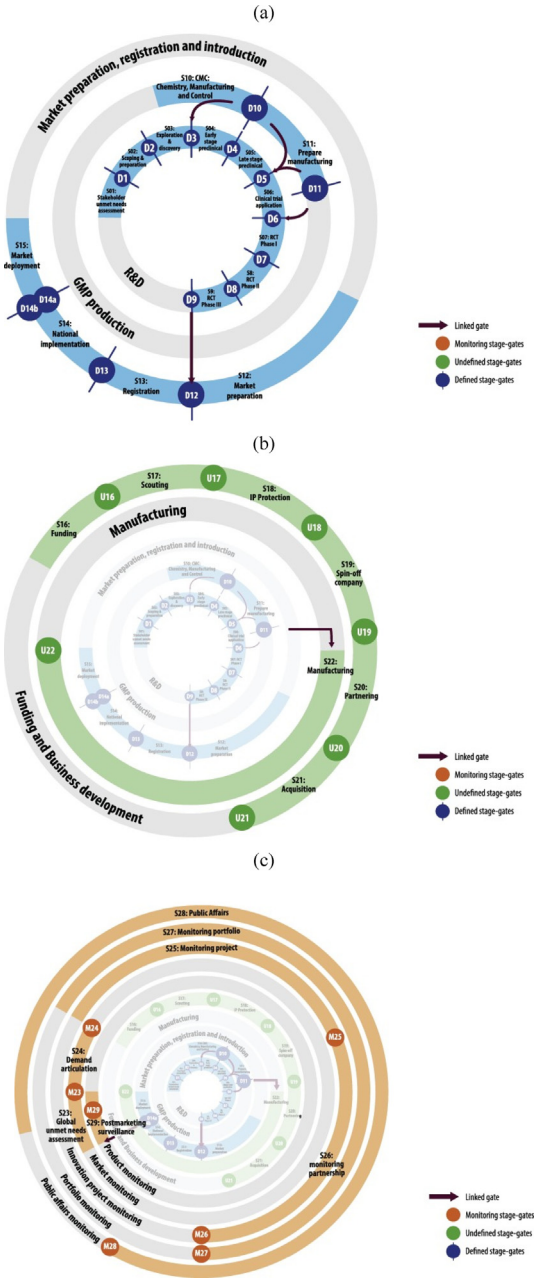

Fig. A1. Vaccine Innovation Model [13]: (a) Defined stages and gates, which occur in a relatively predictable order and timing; (b) Undefined stages and gates, which their occurrence and timing are contingent on a wide variety of factors; (c) Monitoring stages and gates, which occur continuously and iteratively.

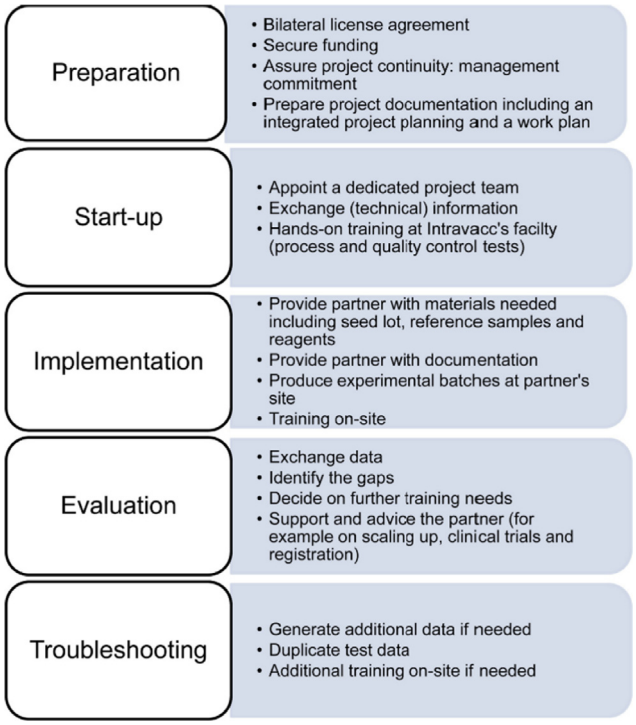

Fig. A2. Hib technology transfer approach [9].

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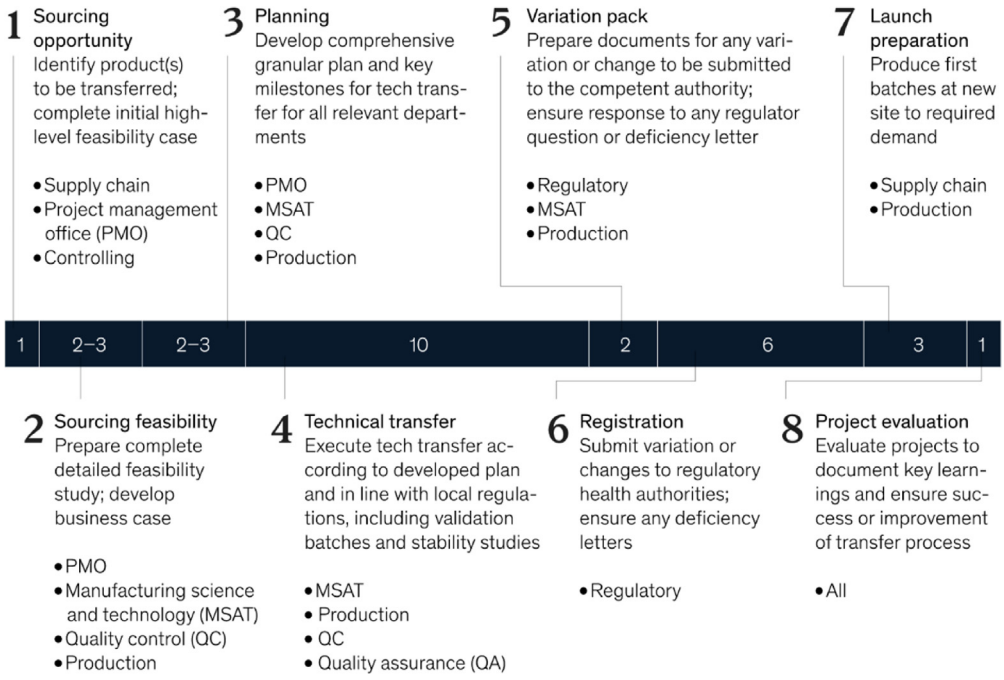

Fig. A3. Technology transfer approach of COVID-19 vaccines [8].

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