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PRODUCT DEVELOPMENT PARTNERSHIPS (PDP) FOR TUBERCULOSIS (TB) VACCINE IN INDIA

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Executive summary

The Tuberculosis (TB) burden across the world is increasing as we speak. With the Covid-19 pandemic disrupting the lives of billions of people since 2019, depriving them of the regular care they receive for chronic neglected diseases like TB and HIV, it has become imperative to ensure that a robust system is in place. This system theoretically should ensure that patients who are under continued monitoring and treatment plans under various government, semi-government and private agencies receive their scheduled treatment in addition to the needs that arise due to a health emergency such as the Covid-19 pandemic.

This is, therefore, an opportune moment to explore newer forms of public-private partnerships since public healthcare systems are under immense stress due to health emergencies. On the one hand, there is a need to ensure uninterrupted supply of medicines and vaccines to those in continuous monitoring and on the other hand, there is a need to ensure that the health systems are sufficiently funded. Product Development Partnerships (PDPs) aim to fulfil the former aspect - ensuring the product availability for those in need, especially in a publicly funded system.

It is with this in mind that the World Health Organisation (WHO) approached us. In line with the agency's work of ensuring vibrant and robust healthcare systems for the most vulnerable across the world, WHO deliberated with us the possible topics to study, including TB and Malaria. Though the initial plan was to study TB and Malaria, due to time constraints, we decided to restrict our study to exploring PDPs for TB vaccine in India.

The main aim of our study is to explore the feasibility of establishment of a PDP for TB vaccines production and equitable access to. To that end, India was chosen as a case study country due to its heaviest share of the global TB burden and continuously increasing number of TV cases. India also has a robust public health system that is often under-funded. Therefore, we decided that it is an area where the practical implications of our study can be tested.

This policy report is based on a structured literature review on PDPs and detail-rich interviews with stakeholders who have experience in the sector and role to play in the fight against TB including prevention and treatment. We have picked experts from across the spectrum, each having their own role to play in the process. The interviews are conducted based on the in-depth questionnaire which are thoroughly tailored per each category of a stakeholder. Interviewed stakeholders represented the following categories: innovative research institutions, governmental entities, PDPs themselves, international and intergovernmental organisations, civil society and philanthropic organisations.

The interviews conducted with the different categories of stakeholders brought us to the idea that it is actually feasible and possible to establish a local PDP for TB vaccine production, however with certain preconditions in place such as increased governmental buy-in, to ensure its operationality and sustainability. It is also worth mentioning that the private sector engagement in financing the TB vaccine production is critical in the establishment and durability of a PDP.

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Introduction

Background and context

In 2020, an estimated 1.88 million persons died due to Tuberculosis (TB) across the world. According to the World Health Organization (WHO), the disease burden was around 10 million persons (TB). HIV, TB and Malaria have been WHO's focus areas since the turn of the millennium. The WHO often refers to the three diseases as 'diseases of poverty and marginalisation', due to its heavy toll on people in the disadvantaged sections of societies. In fact, all three of the above-mentioned diseases are among the top 10 causes for deaths in low-income countries.[1]

Several globally coordinated efforts have been put in place to tackle these epidemics, which have been relatively successful in showing positive results in the reduction of the disease burden. The formation of The Global Fund in 2001 (with the first grants disbursed in 2002) was a milestone in this direction, which encouraged more such efforts to tackle the raging issues of HIV, Malaria and TB predominantly in the Global South. This led to a boost in several privately funded initiatives and public-private partnerships, all with the aim to control the disease burden caused by HIV, TB, and Malaria.

Product Development Partnerships (PDPs) were born out of a necessity to accelerate finding

solutions and improving access to the medicines required to tackle the rising disease burden, especially around HIV in the mid-1990s. PDPs are generally set up as non-profit initiatives born out of collaborations between the public and the private sector. Their main aim is to develop new medical products that are affordable to the masses, especially in low-income countries, by tapping into the innovation potential of multiple partners. The reluctance by the private sector to invest in the research and development of global health technologies created a 'fatal imbalance' in the sector, which led to the creation of PDPs whose main objective is to fill the gap in research and development.[2]

The role of PDPs is to research and develop new medical products and technology and improve access to them to those in need, especially in the low- and middle-income countries, where the disease burden is high. PDPs promote the concept of research and development in health as a

[1] State of inequality: HIV, tuberculosis and malaria. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO

[2] Unknown author (2004). Global forum for health research : 10/90 report. WHO drug information 2004 ; 18(3) : 243

global public good by centering their purpose around affordability and accessibility. (Keusch et al 2010).[3]

Some of the successful PDPs around TB are the TB Alliance which receives funding from UNITAID, USAID, the governments of UK, the Netherlands and Ireland, Bill and Melinda Gates Foundation to name a few, the TB Vaccine initiative (TBVi)[4] which is funded by several pharmaceutical companies, universities and research institutes, the Medicines for Malaria Venture (MMV) which receives funds from UNITAID, the governments of UK, the Netherlands, Australia, Switzerland, South Korea, Ireland and European Union to name a few.

One of the major objectives of forming PDPs in major focus areas is to open up access to healthcare solutions for those across the spectrum, which means not using intellectual property restrictions to curb production. However, studies have indicated that PDPs, so far, do not have a template approach in managing intellectual property rights of the products and technology they develop. (Munoz et al 2015).[5]

Literature Review

Product development partnerships (PDPs)

Literature on Product Development Partnerships (PDPs) is significant considering the time the concept has been around. Since the first PDP was launched in the 1990s, there have been ample studies on the various aspects of PDPs - from its organisational structure, funding patterns, lessons on successes and failures to name a few. Studies have also been conducted on specific case analysis of PDPs like the Meningitis Vaccine Project, the Medicines for Malaria Venture (MMV), PATH and International Vaccine Institute, delving deeper into the factors behind the success of these PDPs.

PDPs are collaborations between the private and the public sector institutions and have separate legal characters. They are usually established as non-profit organisations. (Kulkarni et al., 2015). Chataway et al (2010) stated that PDPs are research and development organisations that are formed to bolster innovations in spaces where the private and some sections of the public sector are unwilling to invest and work alone. (Chataway et al., 2010). In yet another

[3] Keusch GT, Kilama WL, Moon S, Szleza´k NA, Michaud CM (2010) The Global Health System: Linking Knowledge with Action—Learning from Malaria. PLoS Med 7(1): e1000179. doi:10.1371/journal.pmed.1000179
[4] Frick, M. (2015). The tuberculosis vaccines pipeline: A new path to the same destination. 2015 PIPELINE REPORT, 163
[5] V. Muñoz, F. Visentin, D. Foray, P. Gaulé, Can medical products be developed on a non-profit basis? Exploring product development partnerships for neglected diseases, Science and Public Policy, Volume 42, Issue 3, June 2015, Pages 315–338, https://doi.org/10.1093/scipol/scu049

paper, PDPs are defined as non-profit organisations that are oriented towards achieving public health goals, especially in the realm of neglected diseases. (Moran et al., 2010). Moran et al (2010) go on to say that the reason behind PDPs targeting neglected diseases in developing countries is the reluctance by large pharmaceutical companies to heavily invest and pull the burden alone. Cheri (2010) suggests that PDPs work the best if focussed on a public health goal or to fill in a technological or medical gap identified in addressing the public health issue. (Cheri, 2010). PDPs are also seen as the missing piece in the puzzle of addressing the burden of neglected diseases across the world, but especially in developing countries. (Muñoz et al., 2015; Billington, 2016).

The first PDPs were established in the 1990s (Mahoney, 2011) and since then the ecosystem has only grown. Research states that, over the years, PDPs have played a rather important role as a central broker in getting all the necessary agencies to collaborate towards medical innovation. (Hoogstraaten et al., 2020; Huzair, 2012). Since PDPs do not have commercial interests as their guiding light, they have also contributed a richness to disease and drug discovery. (Burrows et al., 2014)

As the PDP space expanded year on year, studies have also moved to delve deeper into specific PDPs, analyse the reasons behind their successes and failures and outlining the lessons to be learned from them. For example, Bishai et al (2011) has studied the workings of the Meningitis Vaccine Project, one of the earliest PDPs in Africa. The authors attributed a big share of the PDP's success to a 'lattice of independent partners' or 'honest brokers' within the system and changes in the public health environment in the developing countries. (Bishai et al., 2011). Similarly, Mahoney (2011) has studied the workings of three PDPs - the Medicines for Malaria Venture (MMV), PATH and the International Vaccine Institute with four of their products in detail to arrive at the success formula behind popular partnerships. The research question of Mahoney's study was what the aspects PDPs should aspire to fulfil if they want to be successful in promoting affordability/access, innovation and disease eradication. The study zeroed in on six determinants of success namely research and development, national markets, international markets, manufacturing, regulatory systems and intellectual property management, for PDPs to achieve their goals. (Mahoney, 2011). Pratt and Loff (2013), in a similar study, examined the strategies deployed by three PDPs – MMV, Drugs for Neglected Diseases initiative (DNDi) and the Institute for One World Health – on the aspects of adoption, availability and affordability of the products they develop. (Pratt & Loff, 2013). They concluded that for PDPs to emerge successful in low- and middle-income countries, they need to focus on health concerns that are a priority in those countries. The study uses the Frost and

Reich framework to evaluate eight drugs (products) introduced to the market by these three PDPs on the aforementioned three aspects. Pratt and Loff (2013) also concluded that PDPs in these countries should also function as vehicles that will set up a robust system in those countries, which will eventually equip them to manufacture medicines themselves without having to depend on high income countries.

PDPs primarily attract funding from donors and philanthropic foundations. They do not have an obligation to the donors like 'for profit' ventures do since the donors are generally interested more in the end result of how their funds are used. (Muñoz et al., 2015). G-Finder studies provide annual updates on the funding received by PDPs worldwide. As per the latest report published by G-Finder on the funding status in 2020, a total of $3,937 million has gone into investment for global research and development on neglected diseases.[6] Of this, $501million (17 per cent) has been invested into PDPs. The Gates Foundation remains the largest funder towards PDPs in 2020 though the investment by the Foundation in MMV and TB Alliance recorded a decrease of 10 per cent and 13 per cent respectively. Meanwhile, the United States Agency for International Development (USAID) increased its funding to PDPs in 2020 by 13 per cent when compared with the 2019-figures. The top four PDPs – MMV, PATH, TB Alliance and International AIDS Vaccine Initiative (IAVI) – recorded a decrease in the money received in 2020, while Foundation for Innovative New Diagnostics (FIND) found a jump in its funding.

Researchers have also studied the rates of success of PDPs across the years. Meredith and Ziemba (2008) state that since 2000, PDPs have been at the forefront of research and development for around 85 percent of 106 neglected diseases. (Meredith & Ziemba, 2008). They further note that the initial attempts of PDPs have been in repurposing existing drug combinations and using it to tackle the burden of neglected diseases. In a table, they also show that the number of PDPs for drugs and vaccines are almost at the same level. Some studies have also attempted to tabulate products in development based on the stages of their development. (Abuduxike & Aljunid, 2012). Young et al.,(2018) have also tabulated the products that are in development for neglected and poverty-related diseases based on different criteria like the costs involved and the health condition. (Young et al., 2018).

Despite its broad successes, PDPs do suffer from certain limitations. Kulkarni et al., (2015) say that openness and transparency is key to the success of a PDP, which directly implies that even if one factor is not fulfilled then the PDP could fail to achieve its objective. (Kulkarni et al.,

[6]Policy Cure Research (2021). *Neglected disease research and development: New perspectives*. Retrieved December 15, 2022, from https://gfinderdata.policycuresresearch.org

2015). Bishai et al., (2011) have pointed out that one of the main reasons behind the success of the Meningitis Vaccine Project was that the disease itself was terrifying and that the risk in developing a vaccine for meningitis was low. (Bishai et al., 2011). Pratt and Loff (2013), in their paper, state that the existing paradigm of PDPs receiving funds from wealthy donors in developed countries perpetuates research disparities and power inequities between high income countries and low- and middle-income countries. “Financial control and decision-making power within PDPs often rest with first-world head offices and senior staff primarily from the United States and Europe. We recently contended that because most of the PDPs’ investment in research infrastructure and personnel goes to high-income countries, their ability to promote global health equity may be impaired.” (Pratt & Loff, 2013).

The significant literature on PDPs and its various aspects does not rule it out from having glaring gaps. Not many studies explore the successes of products that were newly developed from scratch by PDPs. While studies do explore broad funding sources and contributions, there is not enough work on the operational costs and overheads incurred by PDPs. And finally, not much has been written about the intellectual property management by PDPs on their products. Although it can be understood that this lack of literature on the IP aspects might be a direct impact of PDPs majorly relying on drug repurposing, the gap in understanding of those issues is mention-worthy.

Given the literature on PDPs on a broad scale, it becomes clear that neglected diseases like tuberculosis and malaria in developing countries are the best options to explore feasibility.

Tuberculosis in India

The global number of 1.3 million deaths caused due to TB (as per official declaration) in 2020 was almost double of the deaths caused by HIV/AIDS, which was around 0.68 million. TB mortality has been more severely impacted by the Covid-19 pandemic in 2020 than HIV/AIDS. Geographically, in 2020, most TB cases were in the WHO regions of South-East Asia (43 per cent) followed by Africa (25 per cent) and Western Pacific (18 per cent). The high TB burden countries accounted for 86 per cent of all estimated incident cases worldwide and eight of these countries accounted for two thirds of the global total: India (25 per cent), China (8.5 per cent), Indonesia (8.4 per cent), the Philippines (six per cent), Pakistan (5.8 per cent), Nigeria (4.6 per cent), Bangladesh (3.6 per cent), and South Africa (3.3 per cent) (WHO 2021).

TB can affect anyone, regardless of age or sex. The most affected group is adult men, who accounted for 56 per cent of all TB cases in 2020; by comparison, adult women accounted for 33 per cent and children for 11 per cent (WHO 2021).

The Bacille Calmette-Guerin (BCG) is the only vaccine currently that offers protection against TB. The BCG shows varying efficacy in different age and gender groups, and there are safety issues in immunocompromised patients developing BCG-related complications after vaccination. Therefore, there is an urgent requirement for a new and better TB vaccine candidate for all age groups, particularly adults and adolescents than BCG (Soundarya, Ranganathan, and Tripathy 2019).

India is targeting elimination of TB by 2025 since TB has continued to be the country's severest health crisis. TB kills an estimated 480,000 Indians every year and more than 1,400 everyday. Under-investment by the government, weak programme implementation and management, suboptimal quality of care in the private sector, and insufficient advocacy around TB are challenges. The framework of the National TB strategy, set up by the union government of India, aims to reduce estimated TB incidence rate to 44 per 100,000 and emphasises the partnerships among relevant stakeholders including the government, development partners, civil society, international agencies, research institutions, and private sectors. (Ministry of Health 2017). India possesses the technical know-how, competence and resources to address these challenges (Pai, Daftary, and Satyanarayana 2016). Moreover, some Indian manufacturers are not only contributing to the global supply of the BCG vaccine but also one of them is embarking on developing a new TB vaccine through PDP known as TBVi (Cernuschi et al. 2018).

Research objective and questions

Objective

The objective of this project is to study the factors behind the existing success stories among PDPs and to assess the feasibility of replicating it in India (Southeast Asia region) for TB.

The reason behind picking India as a candidate for the TB vaccine study is that India accounts for 26 per cent of the total TB burden in the world as per WHO's latest Global Tuberculosis report 2021.

This study will help us understand the current challenges on the development of new healthcare products to combat TB and transfer them to the target country. Some of these challenges

include the costs involved in research and development of a new TB vaccine, framing inclusive intellectual property clauses, reducing market entry timelines and funding challenges which affects the affordability of the products.

The results of the study will lay down the feasibility of emulating PDPs' success in the above-mentioned geographical area. The research will consider the accessibility of local markets, the economic stability, the regulatory framework around drug safety and intellectual property and existing infrastructural capacity among other aspects. In addition to the mentioned considerations the research will also touch upon the legitimacy, operationality in terms of financing flows and capacity gaps, as well as the challenges posed for the PDPs on the way of their sustainable expansion and operation in a sphere of TB vaccine production.

Research question

Since the aim of the research is to facilitate the establishment of PDPs on TB vaccine production, we will be trying first to identify already existing successful business models of operational PDPs and to what extent they can be replicated in the selected country. With this research we intend to understand and investigate the local capacities of India for piloting of the successful business models of product development partnerships (PDPs) on TB vaccine production in India.

The main question that we seek to answer through this study is whether it is feasible to set up a PDP in India for TB vaccine production. Our study will take us through the process of setting up a PDP step-by-step, gathering the main challenges and opportunities around vaccine development and the establishment of a PDP. The study will analyse specific aspects like research and development, financing, technology transfer, production capacity and regulatory framework in India to conclude on the feasibility of setting up a TB vaccine PDP in the country.

The subject matter is a priori of the interest of both governmental authorities and community. With the transfer of technology in vaccine production, the knowledge and local capacities of local organisations and communities are going to be increased, thus fostering development of indigenous knowledge for more targeted interventions in the governance of the disease prevention, for better reach as well as less dependence from foreign investments.

The results of our study will be presented in the form of a policy report, with detailed sections on existing literature on the topic, research methodology, analysis and findings.

Research design

With the increasing needs of vaccine affordability and accessibility, the global communities have drawn their attention to PDPs. Our research theory is based on public-private partnerships (PPPs) which have evolved into product development partnerships (PDPs) specially in global health. The concept of public-private partnership varies according to individual PPPs. Our approach of this paper assumes diverse actors at international level when partnership projects involve multinational organisations, governments, international and local private sectors. Ultimately, it aims to strengthen the long-term capacity of the recipient country in the pharmaceutical research and development (R&D) and improve vaccine accessibility through the development of new vaccines. Moreover, since main specific donors and the scope of support are not yet defined, the approach of this paper will be focused on the current landscape of PDP and TB vaccines in the country.

This research aims to conduct the feasibility study on piloting the successful PDP business models in India within local institutions. Firstly, out of the current PDP cases, we will focus on the vaccine development partnerships for Tuberculosis in TBVi. TBVi's case will be explored to develop a framework for new partnership. For the next step, feasibility of PDPs to address Tuberculosis in India will be studied. To clarify the subjects of our feasibility research, in India there are four manufacturers which produce Bacille Calmette-Guerin (BCG) which is currently the only Tuberculosis vaccine. One of them, the Serum Institute of India (SII), already is in a PDP with TBVi. The other three companies are Green Signal Biopharma, BCG Vaccine Laboratory and Taj Pharma. (Cernuschi et al., 2018).

Theoretical Framework

From the literature reviews that we have explored, the hypothesis of our research is that the product development partnership for a new TB vaccine is feasible. The theoretical framework of this paper was developed with five principles

First, Given the concept of PDP, the burden of TB which is one of the most neglected diseases should be addressed in a way of strengthened collaboration among different actors. Second, Given the different efficacy of BCG in gender and nationality, the need of a new TB vaccine is urgent to reduce resistance. Third, While India, as one of the largest leaders in the pharmaceutical industry, is already manufacturing BCG, there is also some effort to conduct clinical trials for a new TB vaccine. Fourth, Given the TB burden in South-East Asia particularly in India, it is reasonable to establish a new PDP for TB prevention in India. Fifth,

along with the Indian government's goal of ending TB by 2025, it is expected to facilitate investment in the TB program and the Indian pharmaceutical industry.

With the understanding surrounding PDP, TB vaccine in India and political interest, this paper explores an opportunity to create a PDP for a new TB vaccine in India by conducting in-depth interviews with expertise in order to bring out related challenges, opportunities to take advantage of, and lessons from other PDP cases.

Ultimately, we believe that the PDP in India will address the global burden of TB in a way that maximises the public benefits by securing accessibility, affordability, availability, and adaptability of a new TB vaccine.

Methodology

Methodology of our study consists of the literature review and structured in-depth interviews. Through the literature review, we explored the current landscape of PDPs surrounding infectious diseases such as TB, malaria, HIV/AIDS. However, while the concept of PDP evolved in the mid 1990s, the literature on the concept is not as rich as one would expect.

Due to the time constraints and the subjectivity involved in assessing the political environment and subsequent obscurity of the data we would have acquired it was decided to change the methodology of the research to better fit for purpose. The research is going to be a qualitative study and will be built on the outcomes of interviews with the target stakeholders in PDP, pharmaceutical industry, international organisations, policy makers, public health governing bodies, representatives of civil society, academia etc. The outcomes of the interviews will be combined and put together with the review of the selected literature to form the statement and answer our main research questions.

The steps involved in our data collection method are as follows:

1. Construct a list of potential participants who can be interviewed for our study.
    a. *We had a list of 53 participants, grouped into eight categories: Government, NGO/Civil society, Philanthropy, Academic/research institutions, PDPs, Pharmaceutical companies, international organisations and others. Most participants have been chosen based on their current designations and their previous work experience in the sector. Out of 53 candidates, we could reach out to 27 candidates. Executed interview status can be found below at Table 1. We put the National Institute for Research in Tuberculosis (NIRT) into Government category considering their works and budgets coming from the Indian Government.*

b. *The gaps in our participants list was filled using a snowball sampling method, wherein we asked our interviewees for more contacts, thus branching out in our sample network and also compensating for those who did not respond to us reaching out to them.*

Table 1. Executed interview status

	Government	NGO/Civil Society	Philantropy	Academic/research institutions	PDPs	Pharma Companies	International Organisation	Total
Interviewed	1	1	2	2	3	0	1	10
Not responded	1	2	2	1	2	2	3	13
Declined	0	0	1	0	0	1	2	4
Total	2	3	5	3	5	3	6	27

2. Frame a structured questionnaire with the aim of extracting rich qualitative data from the interviewees.
   a. *We had a structured questionnaire with 22 questions relevant to PDPs and a semi-structured set of questions relevant to TB.*
   b. *After that, we re-categorised it based on stakeholders and refined the questions, in order to bring down the number of questions to fit in our interview time.*
3. Contact interviewees for interviews.
   a. *We started emailing interviewees from November 1, 2022, requesting for a convenient time for the interview. We briefed them about our project and in one case even held a pre-interview briefing call with a representative from the organisation, along with Dr Matthias Helble, our WHO representative. We used the WHO and Geneva Graduate Institute brands in our email subject lines to increase the response rates.*
   b. *We set the interviews for a maximum of 45-60 mins on video call. We used the Webex platform for most of the interviews. For some interviews, the interviewees set up an MS-Teams call and shared it with us. We recorded the interviews conducted via Webex with the consent of all the participants. The call recordings are available on our Webex accounts, which adhere to Europe's GDPR. We have exercised caution while handling recorded data from interviewees.*
   c. *The team then reviewed each call after the interview and debriefed, transcribed and added the data points to a spreadsheet we maintained collectively. We also went back*

to the transcription to ensure that the data added to the sheet is accurate and not misrepresented or misquoted.

4. The data thus collected was compiled and analysed to bring out key findings related to our research question.
5. We have distilled the findings into a set of recommendations which will then be laid out in the form of a policy report and shared with WHO.

Findings

Role of stakeholders in the PDP process

Public sector research institutions

The National Institute for Research in Tuberculosis (NIRT) in India, a premier research organisation affiliated to the Indian Council of Medical Research (ICMR) comes in at the early technical stage or in a later technical stage when they have a candidate and clinical trials need to be designed and conducted. They do not have anything to do with marketing or uptake assessment roles because NIRT and ICMR are scientific organisations. Their role is to provide scientific capacity support in development of a TB vaccine and testing its efficacy.

Private sector

We categorise a variety of stakeholders like PDPs, funding agencies, pharmaceutical companies etc under this umbrella term. Private sector's role is crucial because the initiative to take risk (in innovation) is high in the private sector, as we have seen recently during the Covid-19 pandemic. However, from our conversations with stakeholder-participants, we have come to understand that in India, the government bears a major share of the funds and private players like USAID or the Gates Foundation chip in a minimum amount, usually sufficient to pilot a project. The scaling up is usually done on government money.

Product development partnerships

PDPs can accelerate the development of TB vaccine candidates end-to-end in collaboration with scientific and industry partners, including driving innovative approaches into the field, supporting clinical development of promising candidates, collaborating with research networks and communities in high-TB burden countries; as well as through partnering with civil society organisations and global health partners in a way that all kind of partners engage in enabling supportive policies for TB vaccines R&D including equitable access and its advocacy. This

approach potentially generates economies of scale and efficiencies, but also aids in the sustainability of their work in an environment where finances are finite and where doing more with less.

Pricing Management for affordability in PDP can be found upstream. This seems to somewhat and it is still hard to control that. One of the things we found from this research is most developers do want to price products and to make sure access to affordability. There has not been a problem with it while it is hard to enforce that legally in fact with this point. However, it is crucial that the market of TB vaccines makes it amenable with any vaccine tier pricing that would not ensure affordability if it were lost in low-income countries.

Philanthropy & funding agencies

Philanthropic funding is a drop in the ocean, in our case. What these agencies really do is to demonstrate models in limited geography by using government personnel thinking global level standards put that into practice. If it is successful they then force the government to add more budget in the coming years so that the rest of the geographies can be covered with these same ideas.

For example, in 2014, a feasibility study for gene experts in India was introduced. USAID had supported the procurement of 30 machines that were placed across the country because the government of India wanted to understand how it would work and hard to reach areas in urban and rural desert conditions. The feasibility study was so successful that the government of India has procured with their own domestic budget over 1300 machines of gene experts. What philanthropies could do to aid the cause of TB vaccines here is to help roll it out once vaccines are made available or the government is ready to deploy them.

Opportunities

Infrastructure advantage

Though TB care has been implemented in India in several fragmented ways since the 1900s, targeted measures to control TB began in the 1960s with the National TB Control Programme (NTP). In 1993, this programme transformed into the Revised National TB Control Programme (RNTCP), which introduced a new TB control regimen aligned with the international DOTS package in 1997[7]. Because of this early start, India now has a wide TB support structure that

[7] World Health Organization. (2010). *A brief history of tuberculosis control in India*. *WHO/HTM/TB/2010.4*. https://apps.who.int/iris/handle/10665/44408

not only tests and treats TB but also provides community-led monitoring and counselling through its broad network of primary healthcare centres (PHCs).

Similarly, India has had a Universal Immunisation Programme (UIP) since the 1980s that covers around 2.67 crore newborns and 2.9 crore pregnant women every year.[8] Under UIP, newborns are administered mandatory vaccines for 12 preventable diseases that include childhood TB (via the BCG vaccine). This has, over the years, led to setting up of cold chains and other systems in place for similar public health actions. Therefore, the country already has a robust infrastructure in place for delivery of any vaccine in the future on a massive scale.

In the recent past, India has devoted a lot of resources into setting up digital healthcare technology that will improve delivery of public health services far and wide. The government aims to leverage this infrastructure, like it did during Covid-19, for other public health emergencies too.

India also has cutting-edge research institutions - both publicly funded like the Indian Council of Medical Research (ICMR) and the National Institute for Research in Tuberculosis (NIRT) and private establishments like the Bharat Biotech and the Serum Institute of India (SII) - that have spearhead vaccine research and also collaborated with each other when in need. These institutions also enjoy a good reputation globally, thus equipping them with the advantage of partnering with global institutions of excellence to advance science. In fact, India already has several TB vaccine candidates such as VPM 1002 (collaboration with the Max-Planck-Gesellschaft), r-BCG (a recombinant BCG vaccine by SII) etc., that are at various stages of development.

All these combined with a strong civil society support makes India a hopeful region to establish a TB vaccine PDP.

Higher thrust from the government

In 2018, Narendra Modi, the Prime Minister of India, declared that India will eliminate TB by 2025. In our interviews with key stakeholders in India - civil society organisations and PDPs - a common theme that stood out was that there is a renewed positive push towards TB control since 2018. Since the call to end TB by 2025 came from the prime minister himself, there is a lot of political commitment into the activities towards that goal, they mentioned. The government particularly favours developing indigenous technologies like Truenat (a TB

[8] *Immunization: National Health Mission*. (n.d.). Retrieved December 14, 2022, from https://nhm.gov.in/index1.php?lang=1&level=2&sublinkid=824&lid=220

diagnostic tool from FIND), which has been scaled up massively over the last few years, a participant added.

A highly favourable regulatory and government ecosystem in place in India is perhaps the biggest opportunity to expedite the work on finalising the TB vaccine candidates.

As India takes over the leadership of G20 in 2023, opportunities seem ripe for constant advocacy and garnering support for India's own manufacturing activities related to TB vaccines. It is a great moment to even aim for TB elimination in the Asian region, since India plays a major role in distributing vaccines and drugs to other countries in and outside of Asia.

Challenges

Funding

One of the biggest challenges in setting up a PDP for TB vaccine in India, as pointed out by almost all the participants, was the funding. One of the participants from the PDP organisation stated "Vaccine strategy and collaboration is not a big problem compared to funding." Funding towards TB usually has competitors in HIV, Malaria, and now Covid, which contributed towards TB being sidelined again.

Another challenge in funding is that funding agencies are already moving away from PDPs and channelling their money into other things in global health. In such a climate, raising funds for a new PDP will be challenging.

Based on one interview from the PDP entity, they stated "we should acknowledge that overall, for PDPs, the outlook is uncertain given expanding global health priorities and agendas and limited budgets." The interviewee added a relative example for this: the data collected by Policy Cures in their annual report on global funding for R&D for poverty-related and neglected diseases, showcases that funding for PDPs is flat at best, whilst the need for funding is increasing as PDPs advance products through the pipeline, with more entering late-stage development[9].

Data limitation and Clinical trials

PDPs traditionally suffer from an inability to collect comprehensive data. In the current research climate, data is everything. Therefore, adequate preparation in this regard is required

[9] Policy Cure Research (2021). *Neglected disease research and development: New perspectives*. Retrieved December 15, 2022, from https://gfinderdata.policycuresresearch.org

when it comes to a new PDP. This could mean equipping the PDP with data collection structures or integrating it with other data collection mechanisms or organisations.

TB is endemic in India which means that, unlike Covid-19 where a ready-pool of patients were available for clinical trials, it is difficult to find suitable candidates for TB vaccine trials. A participant also mentioned the cumbersome and prohibitive processes in India as a major roadblock in accelerating TB vaccine development and deployment. Hesitancy among the TB-infected population to participate in clinical trials is another major issue, he pointed out. Effective communication to address this reluctance in viewing clinical trials as something done for the greater good and advancement of science is a possible solution.

Lack of focus on TB prevention

A few participants said: Even though there is a market in India where a lot of people are suffering but these are mostly the low-income group, the focus has always been on treatment. The private players invested in drug production and that's because it gets sold. With vaccines, it has always been difficult to get people to vaccinate. Also, since TB is seen as a disease that's not immediately life-threatening, there is a tendency among people to lean more on testing and treating rather than move towards a preventative attitude.

Though there are a few TB vaccine candidates in the picture, the associated costs are high. The government, therefore, is in a position to weigh the cost and benefits of tuning up the broad infrastructure to improve test-treat of TB or to bring in a new approach altogether - prevention. There needs to be clear economic sense for the government to refocus their efforts towards TB elimination into prevention as well.

Another participant added: The problem in India is that linkage between academia, which can actually bring out more vaccine candidates, and the industry, that can produce them, is weak. So far, I have never seen indigenous development of TB vaccines. Maybe the funding is the first reason. Vaccines are part of the research component of the elimination program as well as part of the TB consortium. But the prevention program is not at the forefront of the agenda at present. The "TB elimination by 2025" is emphasised on the low hanging fruit in a sense: contact listing, screening of contacts and TB preventive therapy. Therefore, prevention is emphasised. Vaccines have not been included yet. There was a push at one point in time led by WHO and USAID to develop this technology of Indian genome sequencing by the public sector. Even after three or four years after the announcement of that policy there is very little action on the ground. There has been some sort of capacity building going on in the public sector. But, evidently, there is a gap in translating evidence into policies.

The fragility of supply chains

The fragility of supply chains is a challenge when dealing with products like vaccines, therapeutics and diagnostics. The Indian vaccine market has very few leaders that have huge production capacities. In such situations, it is easy for the government to lose control over pricing due to monopolistic conditions arising due to a single-player dominance. This emphasises the need to have a holistic approach in capacity-building when it comes to vaccine manufacturing and distribution in the country.

Risks and Limitations

Nevertheless, the study has some limitations and risks associated with the project which are to be highlighted further. One of the major limitations and challenges encountered during the development of the research project was the time limitation of nine months for the overall project, which is rather short to study and cover a geographic area as big as India and to reach out to a broader audience of potential stakeholders.

In the course of the initial phase the research project team also faced an issue in matching the timing appropriate for professionals from the field and the experts from relevant organisations for interviews with academic deadlines. While this risk has been mitigated by participating in interviews as single individuals rather than as a whole team, there is a possibility of missing out on extracting finer details on the topic due to human error. The team recognises this limitation and has planned to go through all the transcripts individually.

Due to the relatively new area of study, the research team has limited primary data and has to rely mainly on secondary data collected from the literature on subject matter as well as discussions with international experts in Tuberculosis. Since the study will be based on mainly secondary data, the research team risks having outdated data and making assumptions based on it, which is also a strong limitation. Moreover, given the specific scope and the problem of the research topic, prior research studies that are relevant to our study are also limited.

Another major limitation to our study is the calculated exclusion from analysing the political landscape of India. The political environment in any country is important in any initiative or establishment to consider investing there. However, since political analysis in a limited time could turn out subjective and incomplete, we have chosen to stick with analysing the feasibility under the good faith argument when it comes to the political conduciveness.

There are also limitations in sampling size of the research. The objective and interest of the partner organisation is to investigate the feasibility of a PDP for TB vaccine production in

India. Though, initially the idea was to look into TB and Malaria and conduct a parallel study of similar nature in Nigeria to explore PDP possibilities for Malaria vaccine, it was later narrowed down to limit the study to India due to time constraint.

There are limited local organisations in the domain, majorly financed or owned by international or multinational entities which creates deviations from the initial plan of the research team to examine the local institutional capacities. Further, once the organisations in India are identified, it is possible that there is limited access to the operational data, financing mechanisms of the organisations which may depend also on external factors such as political interest.

During the data collection process, the team also encountered lack of cooperation from participants due to the limited scope of visibility and accountability. This led to our report being devoid of any perspective from a pharmaceutical company on the topic.

Recommendations

Based on the interviews conducted with a diverse group of stakeholders in the PDP ecosystem and our findings, we have identified a set of recommendations. They are as follows:

- The need of the hour is to build trust between the public and the private sector. The first issue is trust between the public and private sector. Organisations from both sides need to find a balance between profit-making and doing public good. Any imbalance in this equation can result in heavy inequities in affordability, which can lead to inequities in access to the medical product, which proves counter-intuitive for setting up the PDP as a whole. Covid-19 vaccine manufacturing and distribution is a great real life example from which we can learn lessons. The public sector establishments including governments must commit to ensuring public health outcomes while keeping the private sector in its good books. This model needs to be in place and working when a TB vaccine comes along.
- PDPs are as efficient as private companies when it comes to conducting clinical trials and getting the job done. Local PDPs can be used by cash-rich, innovation-oriented private companies to design and conduct trials in India, which can then morph into a marketable product. One of the participants said: If the Indian government puts some money into this, it will give the industry some confidence to invest as well. This will, in turn, make the PDP successful. Apart from looking at it from the cost perspective (it is as expensive as private sector funding, no significant cost savings), it would be useful to look at it

from the efficiency perspective. It has been found that PDPs are as efficient as private companies.

- India must ease the regulatory process in relation to new vaccines. As few participants mentioned, there is a huge potential for a TB vaccine for adolescents/adults in India. However, one of the major stumbling blocks they face is the process to get to the next stage in the preclinical/clinical pipeline. The country needs to facilitate easy mechanisms to deal with innovation.
- Effective communication on community participation in the advancement of science is required. India is a conservative society where when it comes to tasks like a clinical trial, the participants' first question is to ask what's their gain from the process. This makes it difficult to recruit participants for clinical trials, which delays the whole process of bringing a vaccine to the market.
- Look into harnessing an existing, established PDP to push the TB vaccine instead of setting up a new one altogether. The PDP space is fragmented, and the funding is finite. A new PDP specifically for a TB vaccine might split the existing share of funding, thus doing more harm than good. Also, an existing PDP might have a strong infrastructure already in place, which can be taken advantage of for pushing the TB vaccine, including considerations around intellectual property management and technology transfer.
- Government should lead the way. Unlike in countries like Kenya, India's public health expenditure is majorly done by the government. Only a minor chunk of the public health funding pie belongs to the private philanthropies like USAID and the Gates Foundation. This would mean that the focus of the government should not waver from tackling the TB incidence burden, so that the funds don't dry up.
- On the other hand, it might also be a good time to explore mixed funding options by allowing external agencies also to pool in money and build it upwards as a sustainable model. Over-reliance on just one source for money is generally a risky approach, and more so in projects involving huge public health outcomes. This mix of funding can be explored at the national level or even at the regional level, as geopolitics is increasingly moving towards a regional collaboration from a transnational collaboration.
- Encourage technology transfers as a workable model to improve access. The initial investment is a pain point for emerging economies like India when it comes to a TB vaccine. In such cases, India can encourage its big manufacturers to negotiate technology transfer agreements, like the one on Covid-19 vaccine with AstraZeneca, which will

speed up the process of getting the vaccine ready and starting inoculation drives. This could also save upfront investment costs and instead help the company focus on production and distribution within a set timeframe.

- The future studies may go further exploring the feasibility, challenges and best ways to establish the PDPs for broader chain of TB vaccine production at regional levels in Asia and other low-income countries too. This may also be extrapolated further to explore PDP possibilities for vaccines and therapeutics for other chronic and neglected tropical diseases like malaria.

Conclusion

India occupies an enviable position to push for TB elimination due to its geopolitical power and immense innovative capacity in-house. With the government itself declaring its intent to eliminate TB five years ahead of the WHO's goal to end TB, the time is now ripe in India to start actively investing resources into mechanisms that'll help the country achieve its goal. A TB vaccine-PDP is one of the many solutions that could help India in its mission.

Routing the recommendations to set up a TB vaccine PDP in India through the Prime Minister's Office is a safe bet since the ruling dispensation is serious about TB elimination. This will open several doors for the PDP including the much-needed political commitment to the project. India is well placed to translate basic biomedical research towards a product-oriented (TB vaccine) outcome in high TB burden countries in the region; from forming regional clinical networks to regulatory harmonisation and ultimately vaccine distribution. It is recommended that such efforts be closely aligned with international efforts, as well as other regional initiatives. With careful considerations for sustainability how could such efforts be leveraged and support TB vaccines.

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