Role of patents in availability and affordability of tuberculosis care technologies

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The present study deals with the role of patents in the availability and affordability of tuberculosis care technologies and identifies the underlying knowledge gaps and scientific obstacles in the development of tuberculosis care technologies.

Keywords: Diagnostics, drug, patent, tuberculosis, vaccine.

PHARMACEUTICALS under patent protection cost more than identical medicines that are off patent[1]. It is a common belief that patent is one of the factors inhibiting access to pharmaceutical treatment, particularly in low- and medium-income countries. Patent protection and the role that it plays in access to pharmaceuticals have been subject to considerable debate and is still a controversial topic among the policy makers[2]. Patent protection is introduced to provide an adequate incentive mechanism to successfully stimulate research and development (R&D). But can patent protection stimulate R&D in the field of neglected diseases, where the problem of under-investment exists. Do patents play a role in hampering the availability and affordability of tuberculosis (TB) care technologies?

Initiatives like patent pools have been extensively used in emerging industrial or electronic technologies, for example, in construction of airplanes, radios, MPEG-2 audio and video compression, and DVDs[3]. It is only recently that patent pools have begun to be the subject of interest among the biomedical community[4]. A well-accounted scenario of patent pooling in the biomedical field has been the creation of patent pool for improving the access to HIV/AIDS drugs. 'Medicine Patent Pool', an initiative of UNITAID, focuses on making products which are already approved for HIV/AIDS, available on favourable terms to developing markets[5,6]. Patent pooling will avert the problem of obtaining license from different patent owners to produce, sell and export antiretroviral fixed dose combinations[7,8]. But patent pooling also invites the problem of 'tragedy of anticommons', affecting R&D and harming clinical and patient access in the long run[9,10]. The driving forces behind the success of the UNITAID medicine patent pool will be the size of the market, the vigorous generic competition and economics of sale in production. But can such an initiative reap similar benefits in the case of TB?

To understand the situation a thorough study is required on the following points: how much TB care technologies and what areas are available at patent level; whether any patent is in force or not; from which geographical regions have these patents been filed and which organization holds considerable number of patents on TB care technologies? The subject of our study is to create a landscape of the TB care technologies through patent data mining. Empirical data on the extent of patenting in TB care technologies can aid in refocusing the discovery and development efforts and identify the underlying knowledge gaps and scientific obstacles in TB care technology development.

Methodology

Patent data was collected from subscription-based database Derwent Innovation Index for the period 1970–2013. The search methodology used for obtaining patent publications was based on keyword searches. The search for relevant patents was conducted using the keyword 'mycobacterium tuberculosis' in the title, abstract and claims fields. The data retrieved was stored in a standard worksheet template. This consisted of about 4075 patent documents, which were then manually analysed and filtered to 3611 patents by removing the redundant and irrelevant documents. The data was then analysed in order to understand product-wise distribution, geographical distribution of patents, patenting trend over time and top assignees.

Results and discussion

To answer the aforementioned queries, anti-TB patent data have been segregated into three categories, i.e. drugs, diagnostics and vaccines. Around 56% of the patents describe technologies related to anti-TB drugs, 32%

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Table 1. Tuberculosis drugs currently undergoing trials

Drug	Technology described in patent	Description	Assignee	Inventor country	Patent application filed in	Granted Status
PA-824	US5668127	Novel bicyclic nitroimidazole-substituted phenyl oxazolidinones which possess antibacterial activity.	PathoGenesis	United States of America	*AU, CA, EPO, JPO, RU, NZ, ZA, IN	*US, AU
OPC67683	US8163753	Invention provides a 2,3-dihydro-6-nitroimidazo[2,1-b]oxazole compound which has an excellent bactericidal action against *M. tuberculosis*, multi-drug-resistant *M. tuberculosis*, and atypical acid-fast bacteria.	Otsuka Pharmaceutical Co, Ltd	Japan	US, AU, TW, ZA, IN, BR, MX, ES, DE, RU, PH, CN, KR, JP, EPO	US, MX, AU, TW, RU, PH, CN, KR, JP
TMC207	EP2005/054893; EP2003/050322	An isolated mutant atpE protein and departing from the said mutant atpE protein, the identification of an ATPase binding domain.	Janssen Pharmaceuticals/Johnson & Jhonson	Belgium	AU, CA, EPO, JP, RU, CN, IL, KP, NZ, NO, ZA, IN	US
BTZ043	US 2011/0160193 A1; US7863268	Generation of new compounds with activity against *Mycobacteria*, as potential new tuberculosis drugs to overcome problems concerning resistance and drug intolerance.	Leibniz Institute for Natural Product Research and Infection Biology E.V.	Denmark	AU, CA, EG, EPO, JP, KR, NZ, PL, RU, US, TW, MX, RU, DE, BR, CN, IN	US, AU, MX, CN, JP, EP
SQ109	US7652039	Methods and composition comprising substituted diamines for the treatment of MTB.	Sequella, Inc.	United States of America	AU, CA, CN, EPO, JP, ZA, CN, IN	US, EP, JP, CN, AU, IN
LL3858	US7763602	A method for inhibiting the growth of drug-sensitive and drug-resistant *M. tuberculosis*.	Lupin	India	AU, BR, CA, CN, EPO, HU, IL, JP, KR, NZ, US, ZA, IN	US, KR, AU
AZD5847	US7141583	Antibiotic compounds containing a substituted oxazolidinone ring.	AstraZeneca	Great Britain	AU, CA, CN, CZ, EPO, IL, JP, KP, MX, NZ, RU, SG, US, ZA, IN	US, MX, DE, AU, EP, KR, CA
PNU100480	US6919329	A method for the treatment of microbial infections in mammals comprising administration of an effective amount of the novel compound	Pharmacia & Upjohn Company/ Pfizer	United States of America	AU, CN, DE, EPO, JP, KR, MX, NZ, US, ZA, MX, TW, IN	US, MX, KR, EP
Moxifloxacin	US6548079	A process for preparing the aqueous formulation comprising moxifloxacin hydrochloride and sodium chloride, and use of the formulation for preparing a medicament for preventing or treating bacterial infections in humans or animals	Bayer Aktiengesellschaft	Denmark	AU, CA, CH, CZ, EPO, HR, IL, KR, MX, NZ, RU, SG, SK, US, ZA, TW, PH, IN	US, AU, TW, MX, NO, PH, IN, EP

*AU – Australia, AT – Austria, BE – Belgium, BR – Brazil, CA – Canada, CL – Chile, CN – China, CU – Cuba, CZ – Czech Republic, DK – Denmark, EPO – European Patent Office, EG – Egypt, ER – Eritrea, FR – France, DE – Germany, GR – Greece, HK – Hong Kong, HR – Croatia, HU – Hungary, IN – India, ID – Indonesia, IL – Israel, IT – Italy, JP – Japan, KP – Korea (North), KR – Korea (South), MX – Mexico, NO – Norway, NL – The Netherlands, NZ – New Zealand, PH – Philippines, PL – Poland, RU – Russian Federation, SG – Singapore, SK – Slovak Republic, ZA – South Africa, ES – Spain, LK – Sri Lanka, SE – Sweden, CH – Switzerland, TW – Taiwan, UK – United Kingdom, US – United States of America, VN – Vietnam.

of the patents describe TB diagnosis methods and 12% describe anti-TB vaccine technologies (Figure 1; Supplementary information, see online). Study of the worldwide anti-TB patents indicates that, beside India, China, Russia and Brazil, most of the potential anti-TB technologies are not protected in TB high-burden countries

Table 2. Tuberculosis vaccine currently undergoing trial

Vaccine	Technology described in patent	Descriptions	Assignee	Inventor country	Patent application filed in	Granted status
rBCG30	US6471967	An immunogenic composition encompassing a recombinant BCG having an extrachromosomal nucleic acid sequence, including a gene, encoding for a *M. tuberculosis* 30 kDa major extracellular protein	The Reagent of University of California	United States of America	AU, CA, CN, EP, JP, RU, ZA, ES, IN	US, AU, RU, DE, IN, JP, EP
VPM1002	US2008/0292656 A1	Novel vaccine composed of *Mycobacterium* cell which comprises at least one recombinant nucleic acid molecule and a biologically active agent encompassing a peptide or polypeptide and capable of eliciting an immune response in a mammal.	Vakzine Projekt Management GmbH	Germany	AU, CA, CN, EP, JP, KR, MX, RU, US, BR, IN	CN, JP
Aeras 402/ Crucell Ad35	US8012467	A multivalent tuberculosis vaccine comprising a recombinant adenovirus and a pharmaceutically acceptable excipient.	Crucell Holland B.V./ Aeras Global TB Vaccine Foundation	The Netherlands	AU, CA, CN, EP, JP, KR, MX, NZ, US, BR, SG, IN	AU, MX, US
GSK M72	US20090123491A	Novel methods for preventing reactivation of active and latent *M. tuberculosis* infections by administering a pharmaceutical composition comprising a nucleic acid encoding a Mtb72f fusion protein.	Aeras Global TB Vaccine Foundation/GlaxoSmithKline	Belgium	AU, CA, CN, EAPO, EPO, IL, JP, KR, MX, NZ, PH, RU, US, BR, IN	EP, AU, MX
MV85A	US7850979	A novel vaccine comprising a non-replicating or replication impaired poxvirus vector, Modified Vaccinia Ankara (MVA), expressing the translation product of a mycobacterial *Ag85a* gene	Isis Innovation Limited	Great Britain	AU, CA, CN, EAPO, EPO, IL, JP, KP, MX, NZ, IL, US, IN	EP
H1-IC31	US7968105	A novel immunogenic composition, vaccine or pharmaceutical composition comprising a fusion polypeptide for preventing, boosting or treating infection caused by a species of the tuberculosis complex	Statens Serum Institute	Denmark	AU, CA, CN, DK, EP, IL, JP, KP, MX, US, ZA, BR, CN, IN	AU, MX, KR, US
H4-IC31/ Aeras-404	US20100015171A1	An immunogenic composition comprising a TB10.4 protein and an Ag85-complex protein.	Statens Serum Institute	Denmark	EPO, WO, IN, HK, CN, CA, ER, US	
RUTI	US2010/0068258	A method for the prophylactic treatment of tuberculosis, which comprises the administration of an immunotherapeutic agent comprising cell wall fragments of a virulent strain of *M. tuberculosis* complex	Archivel Farma SL	Spain	AU, CA, EP, JP, KP, NZ, US, CN, ZA	EP, MX

(Tables 1–3). Our study shows that despite the presence of a good number of upstream patents, subtle TB care technologies are pipelined at the downstream level.

We can draw two conclusions from the above observation, which reflect minimal conversion of patented technologies into commercial products. First, the absence of patented technologies which have the potential to develop into successful commercial products. Secondly, the low profit opportunity associated with the TB care technology market. The first conclusion indicates the lack of adequate amount of fundamental research related to TB care technologies, especially in the case of vaccine and diagnostics methods[11]. In such a scenario, business models that incorporate 'push programmes' that aid research

Table 3. Tuberculosis diagnostic methods

Diagnostic kits/ methods	Technology described in patent	Description	Assignee	Inventor country	National phase filing	Granted status
QuantiFERON	US7608392	An assay and a kit for measuring a cell-mediated response to an antigen using whole blood or other suitable biological samples.	Cellestis Limited	Australia	AU, CA, EP, JP, US	US, AU, JP, EP
TB-SPOT.TB	US7575870	A method for quantitating *ex vivo* a population of peptide-specific immediate effector *T* cells present *in vivo* in a subject.	Isis Innovation Limited	Great Britain	AU, CA, EP, JP, DE, ES	US, AU, JP, EP
MGIT-960 mycobacteria detection system	US5567598	This invention presents methods for detection and evaluation of metabolic activity of microorganisms based upon their ability to consume dissolved oxygen.	Becton, Dickinson and Co.	United States of America	CA, EP, JP, US, AU, DE	JP, EP, CA, US, AU
Fastplaque-response	US5985596	A method for reducing the time of response of an assay for a first bacterium.	Biotec Laboratories Ltd.	Great Britain	CA, CN, EP, JP, US, AU, DE, ES, IN	AU, US, ES, ES, DE, JP
Luciferase/ Bioluminescense assay	US6225066; US6300061	Methods of producing *Mycobacterial* luciferase reporter mycobacteriophages and use of the mycobacteriophages for the rapid diagnosis of tuberculosis.	Albert Einstein College of Medicine of Yeshiva University	United States of America	AU, US, WO	US
Liposomal agglutination card test or TB screen test	US7888037	Diagnostic kit for detecting pulmonary and extra pulmonary tuberculosis comprising a cocktail of purified cell wall-associated antigens of *M. tuberculosis*.	Madhav Institute of Technology and Science, Gwalior, India	India	EP, DK, JP, US, IN, US, DE, JP	EP, DE, JP, IN, US

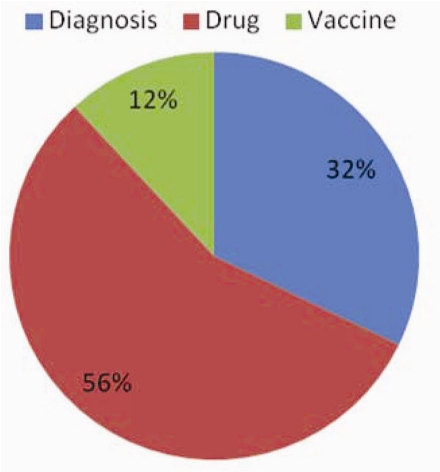

Figure 1. Product-wise distribution of patents (based on published patents).

inputs through direct funding, such as research grants to universities and government laboratories or tax credits to stimulate R&D investment by the private sector, are needed to promote fundamental TB research[12,13]. Underinvestment associated with TB research is another factor which has to be considered in this context. Global TB research remains grossly underfunded, with an estimated funding gap in TB research from 2011 to 2015 being at US$ 6.4 billion[14].

The insufficient profit opportunity associated with the TB market can be considered another reason for the lack of TB care technologies at the downstream level. Investment returns from the TB market are not enough to instigate pharmaceutical industries to invest in patented technologies which have the potential to develop into new drugs, vaccines or diagnostic methods. The cost of developing a new drug is estimated at US$ 115 to 240 million[15]. To be profitable, market prices of new drugs should be relatively high, whereas the cost of the standard regimen is only about US$ 11 per patient[16]. Prahalad[17] considered these low- and middle-income countries offering low profitability margin as 'the invisible opportunity'. The market size in TB high-burden countries is large, but the process of actually reaching the patients is difficult for large firms. In such a scenario, the conventional investment strategies will not work and a single pharmaceutical firm cannot do this alone. The involvement of multiple players, including local government authorities, non-governmental organizations, financial institutions and other companies is required to develop affordable health solution for the poor. In cases where low profitability is the main reason behind the lack of conversion of potential technologies into commercial products, we need innovative business models which incorporate 'pull programmes' that reward the actual creation of the desired drugs or vaccines or diagnostic methods from a patented technology. Pull programmes

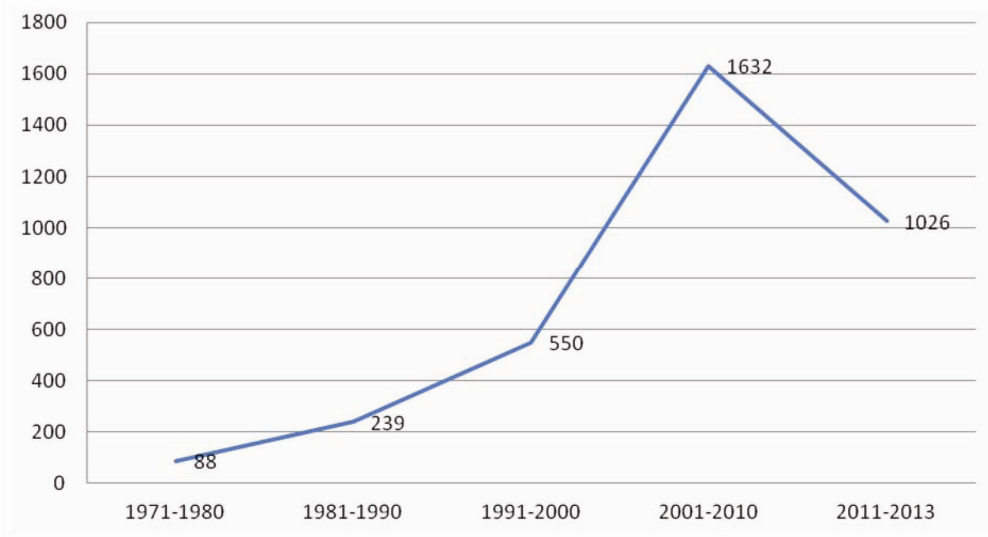

Figure 2. Year-wise distribution of patents (based on publication date).

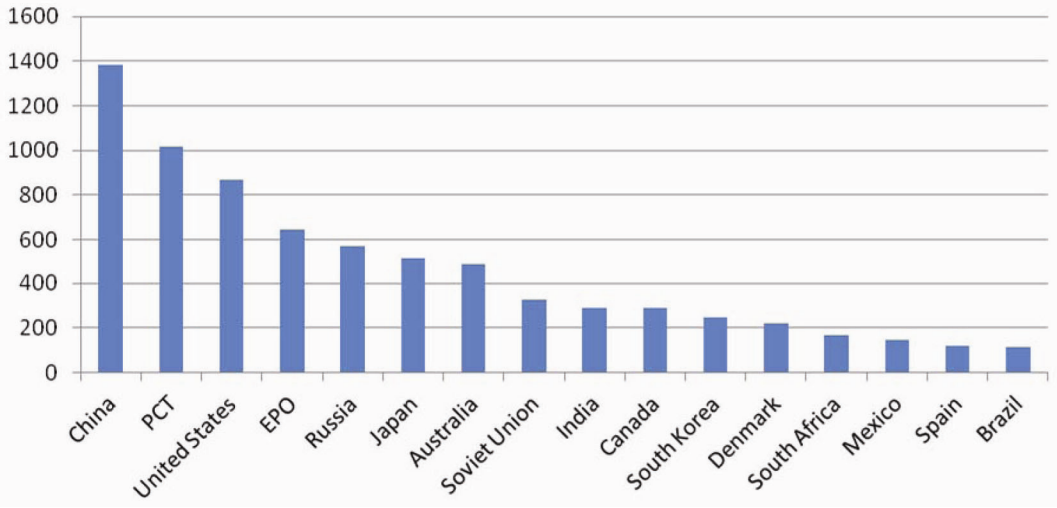

Figure 3. Country-wise distribution of patents (based on publication country).

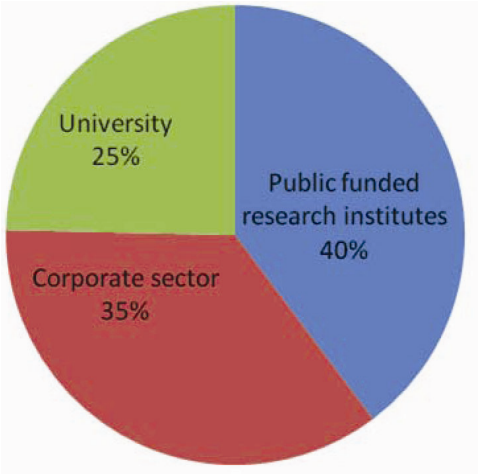

Figure 4. Sector-wise distribution of patents (based on published patents).

such as advanced purchase commitments (the funding for which has to be backed by governments, philanthropists, or innovative financing mechanisms) and patent buyouts have the potential for the establishment of access to affordable drugs/vaccines[18,19]. Pull programmes can also draw the expertise of a large and diffuse set of researchers. Business models which specialize in high-volume, low-margin production, leading to low-cost products are required to make TB care technologies available and affordable to the poor in the developing countries.

Our study spanning four decades, reveals that patenting activity was negligible in the period 1971–1980. The last two decades showed steep increase, for instance, year slot 1991–2000 and 2001–2010 showed 130% and 196% increase respectively. In the last three years (i.e. from 2011 to 2013), the number of patents filed is almost equal to two-thirds of the patents filed from 2001 to 2010. A

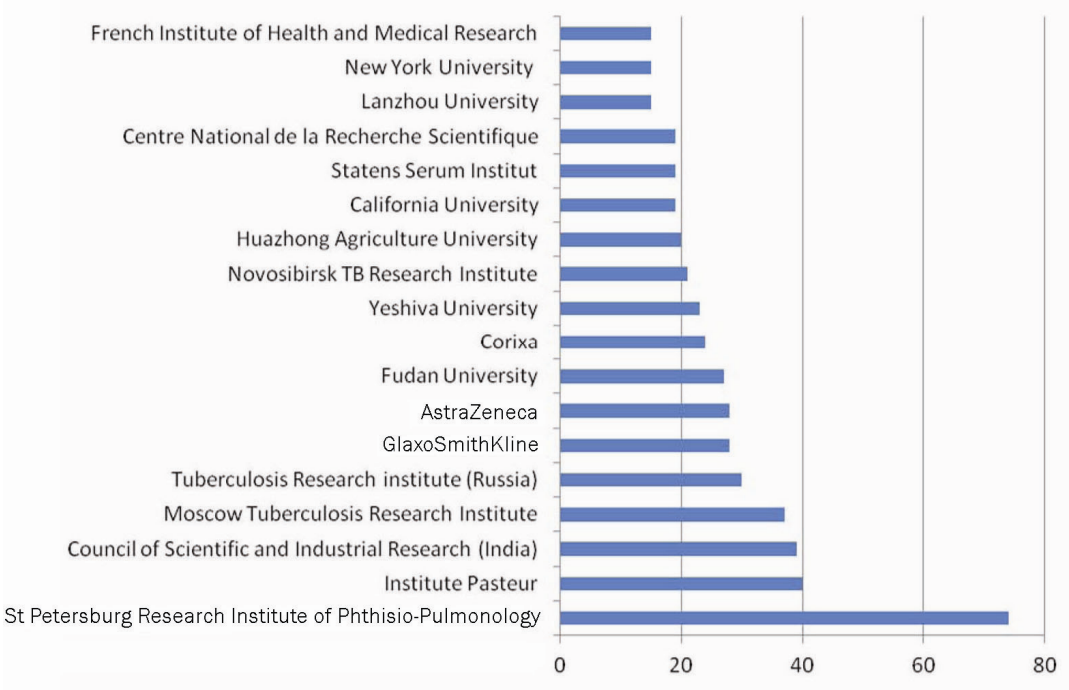

Figure 5. Assignee-wise distribution of patents (based on published patents).

country-wise analysis for the period 1970–2013 showed that out of 16 countries where most of the anti-TB patent were filed (Figure 3), maximum number of patents was filed in China, followed by patents filed through Patent Cooperation Treaty, United States of America, European Patent Office, Russia, Japan and Australia. The patent data was redistributed among corporate, institutional and individual sectors and it was observed that the public-funded research institutes command a significant share with 40% patented inventions. Corporate sector and universities contribute 35% and 25% of the share of total patents respectively (Figure 4). Figure 5 shows the list of assignees who have filed more than 15 anti-TB patents. It can be observed from the list that the top five assignees are all government-funded organizations. GlaxoSmithKline, Corixa and AstraZeneca from the corporate sector also made it to the list of top ten assignees.

Basic research on TB care technologies carried out in the developed world has to undergo clinical trials in developing countries, where maximum number of TB-related cases and deaths occur. So to develop a successful TB care technology, i.e. from basic research to clinical trials to manufacturing and marketing, a smooth coordination among the health sectors of both developing and developed world would be required. To ensure a continued flow of potential candidates into downstream development, discovery efforts must be maintained in a sustainable manner and with active participation of disease-endemic countries[20]. Such a scenario necessitates the use of a business model which will bring together corporate and public sectors of both developed and developing countries. An example of such a model is the product development partnership (PDP), which is non-profit initiative that aims at bringing together public, private, academic and philanthropic sectors to develop technologies for global health[21]. PDP is useful especially in situations where the cost and risk of technology development are too high in relation to the probable market return and when existing technologies are sub-optimal. PDP has been successfully used to develop a meningitis vaccine at less than US$ 0.50 per dose. The meningitis PDP programme started in 2001 and by the end of 2010, manufacturing of the vaccine had started. Basic research for the vaccine was carried out by both public and private sector companies located in USA, aided by philanthropic organizations. Clinical trials were carried out with the aid of both public and private sector institutes located in various parts of the world. Lastly, manufacturing of the vaccine was carried out in the Serum Institute of India Ltd[22]. A similar PDP programme was launched in the late 1990s to develop a TB vaccine. Basic research and pre-clinical trials were carried out by public and academic sector organizations. The vaccine is currently undergoing phase II clinical trial carried out with collaboration of health organizations from Europe and Africa.

Conclusion

In the present situation, patents play no role in the availability and affordability of TB care technologies or in stimulating research in this field. Schemes like patent pools will not be effective because they simplify the

assembly of patent and licensing, but do not necessarily lead to development of technology or market access and distribution[23,24]. Currently, to promote basic research push programmes are needed. Similarly, pull programmes are needed to encourage the corporate sector to develop commercial products. For the success of the push and pull programmes, smooth coordination and collaboration among the private and public sectors are required. It has been demonstrated that public–private mix (PPM) is feasible in TB control in developing countries like India[25]. The potential success of PPM will depend on clear understanding and delineation of the role, responsibility and accountability of both public and private sector actors in the true spirit of partnership, equity, risk-sharing and transparency.

To solve the present problems, a broad set of policies starting from new business model development to open source drug discovery is needed to ensure availability of medicine for this disease. The analysis presented here is not legal advice, but a starting point for independent analyses on business models by independent parties, to make TB care technologies available and affordable at low cost in TB high-burden countries.

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