Opportunities for Canada to Improve Global Access to Medicines

Wojciech Copija, Lauren Degabriele, Mahi Hosseini, Ashley Schram and Liliane Tshiama Kalonji

Edited by Steven J. Hoffman and Lathika Sritharan
Global Health Law Clinic Publication Series
Opportunities for Canada to Improve Global Access to Medicines

April 2016

ISBN 978-0-9951601-2-5 (online)
ISSN 2371-137X (online)

The case studies included in this publication were commissioned by the Office of International Affairs for the Health Portfolio.

Suggested citation for the report

© Global Strategy Lab 2016

Contents of this publication may be reproduced in whole or in part provided the intended use is for non-commercial purposes and full acknowledgement is given to the authors and editors and to the Global Strategy Lab as publisher. Reasonable precautions have been taken to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The publication should particularly not be relied upon for legal advice. The responsibility for interpretation and use of the material lies with the reader. In no event shall the authors, editors or publisher be liable for damages arising from its use.

The case studies included in this publication were commissioned by the Office of International Affairs for the Health Portfolio. Funding for this publication was provided by the Global Strategy Lab. The views expressed here do not necessarily represent the views of the Office of International Affairs for the Health Portfolio, Global Strategy Lab or its partners.

Graphic design and post-production by Tom Jacobs | www.moodmarketing.ca

About the Global Health Law Clinic | www.globalstrategylab.org/clinic
The Global Health Law Clinic is an experiential learning opportunity for students to apply their previous studies to real-world global health practice. Students work in teams to provide a United Nations agency, government, or civil society partner with research, analysis and advice on addressing a pressing global health challenge facing them.

About the Global Strategy Lab | www.globalstrategylab.org
The Global Strategy Lab, directed by Steven J. Hoffman, is an interdisciplinary research program based at the University of Ottawa's Faculty of Law. The Lab brings cutting-edge science and scholarship to bear on how global institutions, instruments and initiatives are designed to better address transnational health threats and social inequalities.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Summary</td>
<td>4</td>
</tr>
<tr>
<td>Introduction</td>
<td>6</td>
</tr>
<tr>
<td>Approach to Selecting Case Studies</td>
<td>9</td>
</tr>
<tr>
<td>Case Study 1: Innovative Medicines Initiative Model</td>
<td>11</td>
</tr>
<tr>
<td>Case Study 2: International Finance Facility for Immunization Model</td>
<td>13</td>
</tr>
<tr>
<td>Case Study 3: Open Source Drug Discovery for Antibiotics</td>
<td>15</td>
</tr>
<tr>
<td>Case Study 4: Drugs for Neglected Diseases Initiative Model</td>
<td>17</td>
</tr>
<tr>
<td>Case Study 5: Bulk Purchasing Schemes to Improve Affordability</td>
<td>18</td>
</tr>
<tr>
<td>Integrating the Case Studies</td>
<td>20</td>
</tr>
<tr>
<td>Applications for Canada</td>
<td>22</td>
</tr>
<tr>
<td>References</td>
<td>24</td>
</tr>
<tr>
<td>Appendix</td>
<td>33</td>
</tr>
</tbody>
</table>
EXECUTIVE SUMMARY

This report explores a number of drug development and delivery models for the Canadian government to consider implementing as it looks to improve access to essential medicines both domestically and internationally. Four market-level case studies focus on innovative financing and collaborative initiatives as ways to enhance Canada’s global standing on pharmaceutical R&D. One patient-level case study considers international legislation as a model to improve Canada’s purchasing power.

In an effort to elicit the most viable options, these five models were selected from a non-exhaustive list of 93 state, non-state, and mixed partnership models, which focused on international financing, collaborations, R&D, and legislation. The Innovative Medicines Initiative (IMI), the International Finance Facility for Immunization (IFFIm), Open Source Drug Discovery (OSDD), Drugs for Neglected Diseases Initiative (DNDi), and Australia’s Pharmaceutical Benefits Scheme (PBS) were specifically selected based on their relevance to Canada’s strong pharmaceutical industry, commitment to R&D and global aid, and domestic health needs. They present alternative models that could be integrated into Canada’s current development and delivery framework to make medicines more readily available and affordable.

IMI and IFFIm present alternative financing models: the IMI model generates funding for R&D activities through resource-sharing partnerships, while the IFFIm model enhances the efficacy of financial commitments through global financial markets. The OSDD is a collaborative model that promotes quick and cheap R&D, and is optimized when coupled with a Product Development Partnership (PDP). DNDi is an example of a PDP, which brings new drugs from the discovery stage to the market. While the four market-level models could bring new drugs to the market at more affordable prices, patient-level interventions are still needed to ensure the affordability of all medicines. The final case study presents the financial benefits accrued through bulk-purchasing and national pharmacare programmes, and Australia’s PBS is explored to this effect.

Taking political and financial feasibility into account, certain models proved to be more viable than others. The IMI is not an ideal model for improving access to medicines in the Canadian context, largely due to its lack of transparency and its prioritizing of the pharmaceutical industry’s interests and commitments. IFFIm and OSDD, on the other hand, do offer innovative mechanisms for improving the efficiency of global health aid and for driving R&D in high-priority global health areas. PDPs are the most valuable model for the Canadian context because PDPs incorporate collaborative funding and development models, while also reflecting domestic and international health priorities. Australia’s PBS may assist in finding an appropriate model for a much needed bulk purchasing scheme.

While the Canadian government should consider partnering with the four market-based organizations, Canada’s current role as an active Gavi funder makes IFFIm the most suitable partner for collaboration; IFFIm may enable Canada to improve its current financial commitments to global vaccination programmes. DNDi is a potential partner that could enable Canada to improve global access to medicines for neglected diseases. Finally, IMI and OSDD are less suitable partners due to IMI’s European-centered mandate and OSDD’s India-based operations.
INTRODUCTION

This report first identifies access to medicines as a major global health concern—exploring the dimensions of the problem internationally and domestically, and briefly highlighting Canada’s commitments and priorities in the area. An overview outlines significant global players and their corresponding actions or strategies in confronting the multifarious barriers preventing equitable and reliable access to medicine. In addition to providing a general assessment of the relevant institutional frameworks, legal environments, policies, proposals, key stakeholders, and emerging issues, this section is the origin of the five case studies that follow. This report includes detailed analyses of five major pharmaceutical development and delivery models—IMI and IFFIm financing models, OSSD and DNDi collaborative models, and Australia’s pharmacare model—and an assessment of their respective viabilities for implementation. The concluding section integrates these individual models to provide a composite alternative to Canada’s current development and delivery framework, one that could bring new drugs to the market more efficiently.

A detailed Appendix, including a comprehensive methodology and a high-level overview of the principal themes emerging from the access to medicines literature review, supplements this report. An extensive Web Appendix includes illustrative actor-action network maps, an actor-action dyad extraction table, as well as corresponding summaries of the numerous access to medicines initiatives explored.

Access to Medicines in Canada and Globally

According to the World Health Organization (WHO), “a well-functioning health system ensures equitable access to essential medical products, vaccines, and technologies of assured quality, safety, efficacy and cost-effectiveness” [1]. Measured against this standard, a majority of the world’s health systems are found lacking as they fail to provide their citizens with access to the most essential health products and services [2]. While health is one of the fastest growing sectors in the world’s economy, the distribution of the benefits of this growth is grossly inequitable. Although developed countries generally enjoy adequate healthcare standards, high prices render certain essential medicines virtually inaccessible for significant segments of society. Access to essential medicines is an even greater problem in developing countries, where the most fundamental healthcare needs of citizens are regularly eschewed. Improving access to essential medicines is a priority for all countries as they combat deficiencies in their domestic healthcare systems and contribute to efforts to reducing mortality rates abroad.

The global discourse surrounding access to medicines is complex and evolving. It involves a diverse range of private and public sector voices and perspectives, including those of governments, healthcare providers, international institutions, pharmaceutical and biotechnology companies, regulatory authorities, and patient organizations. There is increasing consensus that collective action is required to improve the availability and affordability of existing medicines, as well as to develop new pharmaceuticals to address pressing global health needs, including the issue of antimicrobial resistance.
As such, individuals, organizations, and countries are increasingly forging productive partnerships, and confronting barriers that operate to limit access by leveraging their respective strengths in innovative ways. The pooling of resources and knowledge allows these partnerships to address inefficiencies of administration, distribution, and quality control, and curtail the exorbitant costs of new product development and production [3]. Collaborations range from innovative research and development initiatives, legislative and regulatory reforms, and awareness campaigns, to capacity-building investments, and creative funding schemes and pricing strategies [4].

Improving access to medicines, both domestically and globally, has traditionally been, and continues to be, an important part of Canada’s mandate. For example, between 2001 and 2010, the Canadian government contributed over $900 million to the Global Fund to Fight AIDS, Tuberculosis, and Malaria, ranking seventh among individual country donors [5]. In 2004, Canada became the first country to pass access to medicines legislation, like Canada’s Access to Medicines Regime (CAMR), allowing the legal production and export of generic drugs to countries without manufacturing capacity.

Despite this legislative success, CAMR was only implemented once to send a shipment of antiretroviral drugs to Rwanda [6], suggesting that Canada’s competitive strengths do not lie with the production of generic drugs.

Instead, a federally appointed commission recommended that Canada take advantage of its positive relationship with developing countries and capitalize on its research and development (R&D) capacities to improve global health [7]. Focusing on its strengths, Canada has a major opportunity to both improve access to medicines and enhance its global standing on healthcare related issues, while also reinforcing its economy.

This report identifies a broad spectrum of global activities designed to address the challenge of increasing access to medicines, and to advise on the viability of the implementation of these activities given the present Canadian political climate.

**Landscape of Access to Medicines Initiatives**

The initiatives directed towards improving access to medicines are innumerable. In an effort to comprehend the myriad interactions between international actors, 93 unique global actors and actions were identified for review (see Appendix for detailed methodology). 39 actions were led by state actors, 11 actions were led by non-state actors, and 43 actions were led by mixed partnership models (most commonly in the form of public-private partnerships or intergovernmental organization and non-state members). A table in the Appendix provides count data for the dyads by access to medicines area, action type, and actor type. The most common types of actions include financing (n=26) and collaborations (n=23). Thematic areas of access to medicines most frequently targeted included multidimensional efforts (n=32), R&D (n=23), and access to a delivery of treatment (n=21). Figure 1 (and Figures 10 through 16 in the Web Appendix) provides a visualization of the results by each of the thematic areas identified, and reveals gaps, which point towards opportunities for future action. Refer to the Web Appendix for summary information for each dyad,
including the type of actor, actor name, type of action, action name, the area of access to medicines addressed, whether the action was proposed or implemented and when, as well as a brief description of the aim of the action.

The findings have been further broken down into seven distinct action categories. These categories include: campaigns, financing, frameworks, legislation, programmes, global action plans, and collaborations. Campaigns typically implemented significant strategies developed to promote awareness, raise funds, develop and disseminate research and information, and engage stakeholders in combatting HIV/AIDS. In financing, the research revealed numerous strategies conducted by both state and non-state actors concerning efficient procurement, pricing, competition policies, allowance of generics and compulsory licensing, and reimbursement programs for those who cannot pay and domestic manufacturing capacity [8]. We have observed a rise of public-private partnerships engaged in innovative fundraising as a response to the need for sustainable financing. For example, the Global Health Innovative Technology Fund (GHIT) provides funding for medicines, diagnostics and prevention of HIV/AIDS, TB, and malaria [9]. Additional results from figures highlight different interactions among states and non-states. For example, Figure 1 above identifies key actors in financing, including the Global Health Innovative Technology Fund and UNITAID, as well as well-supported financing actions, including the Pneumococcal Advance Market Commitment and other promising initiatives with fewer connections, such as the Vaccine Investment Strategy. Figure 11 in the Web Appendix, however, suggests there are fewer initiatives enhancing domestic capacity in South Africa and Brazil.
The results for frameworks highlight collaborative efforts guiding future global initiatives in the financing and procurement of essential drugs. Our review has revealed few actions targeted to improving global health aid. Figure 12 in the Web Appendix shows that the Equitable Access Initiative (EAI) is a well-supported effort. This initiative identifies the needs and constraints surrounding equitable access to health, including medical technologies and medicines for countries transitioning from LMIC status [10]. In the same figure, the E-Marketplace [10], which allows the purchase of various medicines and health commodities, presents less support. The results under legislation underline legislative reforms adopted to address intellectual property and patent law barriers, as well as to promote universal health care coverage and to fight the proliferation of counterfeit drugs. Although it was used once, CAMR provides a framework through which some of the world’s poorest nations are able to import less expensive generic versions of patented drugs [5]. Figure 13 in the Web Appendix illustrates that non-state actors and BRICS countries are lead actors in this area. Global action plans guide WHO member states in achieving international health targets. For example, the 2014 Global Action Plan proposed by WHO aims to combat antimicrobial resistance [11]. Programmes aim to influence the development, procurement, and distribution of essential medical products and services. The Drugs for Neglected Disease Initiative works to develop new treatments and new formulations of existing drugs for neglected diseases [12], while the Innovative Medicines Initiative (IMI) aims to improve health by speeding up the development of, and patient access to, next generation vaccines and antibiotics [13].

Most collaborations are centered on R&D initiatives that aim to promote research to improve international health, IP laws, and response to global threats. We have observed that the Global Health Security Initiative appears to be an integrated action while other actions, such as the Vaccines Research Relief, remain country-specific. This may be an opportunity for better inter-country cooperation (see Figure 15 in the Web Appendix).

**APPRAOCH TO SELECTING CASE STUDIES**

Although the global conversation surrounding access to medicines is complex and largely unresolved, innovative programmes and funding efforts, creative R&D actions, and collaborations demonstrate an international commitment for improved global health. Canada plays a significant role in the international effort to improve global health. The Canadian government provides support to the Global Alliance for Vaccines and Immunization (Gavi); the Pneumococcal Advance Market Commitment; and the Global Health Security Initiative. Canada is also a member of and contributes to the United Nations, World Health Organization, the World Bank, and the Organization for Economic Cooperation and Development. Domestically however, efforts to improve access to essential medicines are also necessary. Accordingly, we focused on actions that aim to develop new medicines, primarily international efforts that have an impact on the domestic level. Toward this end, an integrated case studies model was adopted to situate these initiatives against the full complexity of the health system to understand how these efforts connect and impact national and international health systems (see Figure 2 for integrated case studies diagram). This approach reflects the many ways through which access to essential medicines can be enhanced.

We reviewed a list of actions designed to improve access to medicines to elicit a number of viable options for international action on this issue. Additionally, we utilised network graphing as a data visualization technique to appreciate the interconnectivity among actors and actions within each map as captured in the report. The action-actor map revealed how integration may vary between areas, which may highlight redundancies within the system and the gaps in actors and actions in certain areas of access to medicines that could be addressed. After generating our list of initiatives, we consulted Canadian government officials to identify five options that could be most relevant to Canada’s health needs, and ultimately purposively chose the following to maximize insights across a range of options:
Innovative Medicines Initiative Financing Model (IMI)  
a public/private partnership European initiative working to  
 improve health by speeding up the development of, and  
 patient access to, innovative medicines, particularly in areas  
 where there is an unmet medical or social need. Currently  
in its second phase, IMI 2 programme seeks to develop next  
generation vaccines, medicines and treatments, such as new  
antibiotics.

International Finance Facility for Immunization (IFFIm)  
an innovative financing mechanism working to rapidly  
 accelerate the availability and predictability of funds  
 for immunization. It uses donor government pledges as  
 security to sell bonds in the capital markets, making funds  
 immediately available for Gavi programmes.

Open Source Drug Discovery for Antibiotics (OSDD)  
to provide affordable healthcare to the developing world  
 by providing a global platform for collaboration on solving  
 complex problems associated with discovering novel  
 therapies for neglected tropical diseases.

Drugs for Neglected Diseases Initiative (DNDi) A Product  
Development Partnership Model  
a collaborative, non-profit drug research and development  
 organization that develops new treatments for neglected  
diseases.

National Pharmacare Model  
Bulk Purchasing Schemes to Improve Affordability – the  
 pan-Canadian Pricing Alliance works to unite the country  
to utilize combined purchasing to increase access to drug  
treatment, lower drug costs, and improve drug coverage  
consistency. Australia’s Pharmaceutical Benefits Scheme  
(PBS) serves as a model that demonstrates how federated  
states can collaborate to lower drug costs and improve  
affordability.

Case studies were conducted on each of these selected  
 processes. These case studies led to the five key  
 recommendations made in this report. In performing our  
 research, we analyzed three main areas: performance  
 indicators (i.e., health implications and political feasibility);
implementation considerations (i.e., financial feasibility); and the viability of each option for Canada. In particular, we examined each initiative’s purpose, their respective implementation challenges, and actual outcomes. Such an analysis generates some strong options for Canadian decision-makers to act upon.

We found that each case offered distinct insights that will inform key stakeholders on medicines policies and programme strategies. For instance, financial initiatives like IMI and IFFIm improve global health aid by providing strategies for lowering medicine prices as well as alternatives to the traditional patent protection system. And innovative PDPs and open source development models, such as DNDi and OSDD promote and create incentives for pharmaceutical R&D, generate new products, and build domestic capacity. Finally, bulk-purchasing schemes like the PBS improve access and delivery of treatment.

CASE STUDY 1: INNOVATIVE MEDICINES INITIATIVE MODEL

Launched in 2008 as a joint venture between the European Commission (EC) and the European Federation of Pharmaceutical Industries & Associations (EFPIA), the Innovative Medicines Initiative (IMI) is the world’s largest public-private partnership (PPP) in the biomedical and health research industry [14]. Created to address escalating costs and declining productivity in pharmaceutical research and development [15], IMI has focused its attentions on developing essential medicines and prioritizing the healthcare challenges for Europe as outlined in the WHO priority medicines report [16]. Responsive to the growing evidence that R&D can benefit from the broad sharing of assets, tools, and expertise across multiple sectors [17], IMI’s mission to facilitate pharmaceutical innovation is advanced by implementing openly collaborative endeavors between actors in the pharmaceutical industry, academia, small and medium enterprises (SMEs), regulatory authorities, and patient groups [18]. As such, IMI has actively embraced a research-by-consortium framework that leverages the collective intellect and resources of stakeholders to optimize the development of medicines, diagnostics, and new tools for predicting drug safety and efficacy [19].

Financing Model

IMI is funded jointly by the EC and EFPIA, with both founding members equal in terms of their level of investment and rights. For the IMI 2 programme (2014-2024), the total budget is €3.3 billion, half of which comes from Horizon 2020, the EC’s framework programme for research and innovation (see Web Appendix 3-1.1 for an overview of Horizon 2020), and the other half from EFPIA-affiliated pharmaceutical companies and other industry partners. EFPIA companies contribute to the projects in the form of ‘in kind’ contributions by committing human resources, providing access to data sets, samples, research facilities and equipment, and sometimes through direct monetary contribution. These contributions are invaluable as they bring together the expertise of individuals working in industry with the expertise found in other organizations. Recipients of IMI funding include universities and research organizations, patient and non-profit organizations, as well as regulatory agencies and SMEs [14,18].

Among the conditions for participation in an IMI 2 consortium is that it be composed of at least three legal entities, each established in a different EU member state or associated
country [20]. This condition encourages the creation of novel partnerships, leading to new commercial possibilities, as well as broader capacity building and knowledge sharing.

**Project Development and Implementation**

The feature that differentiates IMI from other PPPs is that pharmaceutical companies have priority in identifying areas they want to invest in; only then are the EC and IMI committees consulted and topics further refined to address priorities. IMI’s role, then, is to work on the context and to coordinate with the other major partners [21]. The rationale for this model is that it most efficiently “addresses gaps and bottlenecks in the drug development process by combining the traditional strengths of industry (management organization and technology) with those of academia and small businesses (creativity, innovation, and entrepreneurship)”[19].

Once a drug has been developed, it must pass through a series of clinical trials and be approved by regulatory authorities, such as the European Medicines Agency (EMA), insurance companies, and national health authorities, which delays the process. IMI’s coordinating function facilitates dialogue between industry and these regulators; the result being that they generate ideas and monitor advances more closely together, which ultimately results in quicker regulatory approval. In fact, over half of IMI projects have regulators either as partners or advisors.

**Performance Indicators**

IMI reports successes on numerous fronts: the IMI model has fast-tracked the clinical development of new antibacterial agents against Gram-negative bacteria, created the largest known database of studies on schizophrenia, and made advances to our understanding of first-world diseases, including cancer, diabetes, Alzheimer’s and other neurodegenerative diseases [22,23], to name just a few.

Additionally, bibliometric analyses reveal that IMI-affiliated authors produced over 750 publications by 2014, with over 26% identified as “highly cited,” meaning they belong to the world’s top 10% in their journal category. IMI ranked first (amongst similar PPPs) in terms of the citation impact of published articles [23], which is evidence of the scientific excellence of its research.

This model is not without its detractors, however. The principal complaint is that the model suffers from built-in conflicts of interest, which are manifest in an increasing disconnect between essential medicines and areas in which industry is willing to invest, and in the lack of parity between the academic and pharmaceutical research communities. Other complaints propose that IMI research diverges from WHO goals, that control mechanisms lack transparency, and that the financing model essentially works to subsidize the pharmaceutical industry via taxpayer-sponsored research grants [24].

**Implementation Considerations**

IMI acknowledges that to continue as a viable engine for regulatory science, it will increasingly have to develop scientific collaborations with PPPs on a global scale. Indeed, to assemble a critical mass of resources and expertise outside of Europe, IMI has already partnered with a number of US-based institutions, including the Critical Path Institute [19,25] and is evaluating new initiatives developed in Japan and South Korea.
[18]. However, given its European-centered mandate, not to mention its operative and legislative frameworks, it is unlikely that IMI would create a partnership with a foreign government such as Canada.

On the other hand, the Québec Consortium for Drug Discovery (CQDM), a Canadian PPP using a collaborative R&D model similar to that of IMI, and striving to expand its international networks also [26], might be just the sort of partner that IMI is looking to collaborate with.

**CASE STUDY 2: INTERNATIONAL FINANCE FACILITY FOR IMMUNIZATION MODEL**

Gavi is a public-private global health partnership working to increase child immunization rates by facilitating access to new and underused vaccines. Immunization is widely considered one of the most cost-effective ways of reducing child mortality rates and improving living health standards [27]. Since launching in 2000, Gavi support has contributed to the immunization of an estimated 500 million children in 73 of the world’s poorest countries. To date, Gavi has received financial support from public and private donors amounting to over US$10 billion, including commitments up to year 2020 [28].

**Financing Model**

In 2006, Gavi incorporated the International Finance Facility for Immunization (IFFIm) to scale up rapidly in order to meet immediate and urgent needs. IFFIm is an innovative financing mechanism designed to accelerate the availability, flexibility, and predictability of funds for Gavi by transforming long-term, legally binding government pledges into immediately accessible cash resources [29]. It does so by using donor commitments from various countries as security to issue ‘vaccine bonds’ to investors in a variety of currencies and international capital markets (see Web Appendix 3-2.1 for additional information on IFFIm’s Vaccine Bonds). This arrangement allows IFFIm to accelerate the availability of funds (this process is known as “frontloading”) and use legally binding donor commitments to provide financial resources to Gavi when they are most needed (see Figure 4 for IFFIm funding structure). Countries have pledged to provide more than US$6.3 billion to IFFIm over a multi-year commitment (most are twenty years) [30] (see Web Appendix for a list of countries that have entered into Grant Agreements with IFFIm to make long-term financial pledges).

**Performance Indicators**

Although IFFIm is the first aid-financing mechanism in history to use irrevocable financial commitments from sovereign donors to raise funds in the capital market, the concept has proven successful. As of January 2016, IFFIm has contributed US$2.5 billion to Gavi to fund vaccines and other programmes, and IFFIm’s vaccine bonds have raised US$5.2 billion on the capital markets since 2006 [28]. IFFIm is currently projected to provide an additional US$1.2 billion to Gavi between 2016-2020 [31]. IFFIm’s vaccine bonds are popular in the capital market, with its latest issuance being 1.6 times oversubscribed [32].

However, due to IFFIm’s conservative gearing ratio, which limits the degree to which IFFIm can leverage its pledges, it is not frontloading as quickly as it had previously been expected to. At the outset of the program, IFFIm established a finance transfer goal of US$3.356 billion by 2015 [33]. Concerns have also been raised about IFFIm’s ability to continue to raise funds at the same rate in the coming years [34].
Since its inception, IFFIm has proven to be financially efficient. Its strong credit rating and the presence of the World Bank as Treasury Manager have enabled it to enjoy a relatively low cost of borrowing. Traditionally, IFFIm’s all-in cost of borrowing has been below the weighted average of that of its donors’ (on average at 14 basis points less than a weighted composite of its donors) [33]. IFFIm is currently comfortably within its targeted financial range. Over IFFIm’s life span, interest rates and costs (operations, etc.) have typically represented approximately 7.25% of the Net Present Value of pledges [33]. Operational costs are estimated at approximately $7 million per year, totalling $150-170 million over IFFIm’s lifetime – representing 4.1 to 4.6% of the present value of current pledges [34]. However, due to IFFIm’s unique business model, no suitable benchmark currently exists to assess whether these figures are reasonable, or within industry standards.

IFFIm has had a significant impact on Gavi spending power. Since 2006, IFFIm has accounted between 43% and 64% of Gavi’s expenditures, enabling Gavi to evolved into a major development actor in global health [33,34]. See Web Appendix 3-2.3 for more detail on Gavi activities funded by IFFIm.

The health impact of IFFIm funded investments is difficult to measure. The majority of IFFIm funded Gavi activities were already underway prior to receiving IFFIm funding and the number of deaths averted depend on various factors, the majority of which are outside IFFIm’s control. According to a cost-benefit analysis conducted by an independent organization commissioned by Gavi, IFFIm would need to avert around 800,000 deaths in order to “break even”. The study found that “even [the] lowest estimates suggest that [IFFIm’s] health impact is likely to far exceed” its breakeven point and that IFFIm has already more than achieved the benefits necessary to justify the total costs in terms of future deaths averted [34].

Implementation Considerations
Supporting IFFIm would reinforce Canada’s long-standing commitment to assist children and youth in developing countries affected by vaccine-preventable diseases. Canada is one of Gavi’s top ten government donors, providing Gavi with $313 million during 2002-2015, and pledging an additional $500 million for Gavi’s 2016-2020 strategy to immunize 300 million children by 2020 [35]. Canada is also a founding donor of the Advance Market Commitment for pneumococcal vaccines, which is another innovative financing mechanisms supporting Gavi. Joining IFFIm would be consistent with these activities [36].

Supporting IFFIm would require Canada to make legally binding pledges, which would prevent future Canadian governments from breaking the current government’s commitments. This could become a controversial point as the vast majority of Canada’s international assistance commitments do not constitute legally binding obligations and they are not legislated [37]. Opposition to legally binding financial commitments was seen most recently during the 2015 Paris Climate Conference, where several countries, including Canada, reportedly firmly opposed provisions that would have made the $100 billion annual pledge to assist developing countries dealing with the consequences of climate change a legally binding commitment [38].
IFFIm has proven to be a successful concept that allows Gavi to implement its immunization programs more quickly. Canada is already contributing to Gavi and joining IFFIm would be consistent with its efforts in this field. And although Canada recently pledged half a billion dollars to support Gavi for the next five years, it could consider allocating a portion of this money to IFFIm, which would be similar to the approach that Australia took when joining IFFIm [39]. This decision could be made in consultation with Gavi.

**CASE STUDY 3: OPEN SOURCE DRUG DISCOVERY FOR ANTIBIOTICS**

The excessive and inappropriate use of antibiotic drugs, alongside a lack of innovation in new R&D, is contributing to an emerging global health crisis [40]. As many as 700,000 people around the world die annually as a result of antimicrobial resistance, a number that is forecasted to rise to 10 million annually by 2050 [41]. The number of new antibiotic patents and approvals continues to drop, and antibiotics receive even less attention than vaccine or rare disease research [41,42]. R&D is currently incentivized through a patent system, where medicine is promoted for as long as possible, to as many people as possible, for the highest cost possible. This system is poorly suited for the R&D of antibiotics, which have a short-term use, require conservation for efficacy, and have low revenues [43].

An open source R&D strategy has been proposed to address this stall in the pipeline [40,44]. The open source movement has its roots in software development [45], and includes the principles of open access, open collaboration, and open rules [46] (see Web Appendix 3-3.1 for an overview of the characteristics of open source software development and the transferability to open source drug discovery). Applying an open source strategy to antibiotic R&D is most applicable in the pre-clinical stages [46], including: (1) basic research, building knowledge of the organism and how it interacts with the human body; (2) target identification and validation, identifying biological and chemical targets to interfere with
the organism; (3) lead identification, identifying compounds that act on those targets; and (4) lead optimization, testing lead compounds in vivo [47,48]. Industry partnerships and product development partnerships (PDPs, see Case Study D) are important in the end stages of drug discovery and in bringing new drugs to the market [49]. Open source discovery is one component of a proposed strategy on addressing antibiotic resistance, the Antibiotics Innovation Funding Mechanism (AIFM), which incorporates innovation inducement prizes and user fees to generate a comprehensive and self-sustaining approach [40] (see Figure 5 for an overview).

India's Open Source Drug Discovery (OSDD)

Several open source drug discovery projects are underway [45], the most prominent of which is India's Open Source Drug Discovery (OSDD). OSDD was created in 2008 to provide a global platform for collaboration on complex problems associated with discovering novel therapies for neglected diseases, focusing on tuberculosis and malaria. OSDD has used volunteer labour to curate publicly available data repositories and annotated genomes to identify the lifecycle of select tuberculosis strains in order to develop and screen potential drug targets. OSDD has effected the key characteristics of open source development, attracting and managing voluntary collaborative participation, while establishing legal and funding structures for open source drug discovery [49] (see Web Appendix for additional information on OSDD).

Performance Indicators

OSDD has generated a volunteer base of over 8,000 people from 130 countries [50]. They host over 240 projects under the guidance of over 180 principal investigators [44]. This project has screened approximately 10,000 new compounds against tuberculosis and malaria and has twelve new targets in lead optimization. It has also developed a new combination regimen for multi-drug resistant tuberculosis currently in Phase II-B trials, which, if successful, would reduce the volume and duration of treatment relative to currently available therapies [50]. OSDD has developed partnerships with 39 academic institutions, 14 industry partners, multiple PDPs, and is engaged in discussions with the WHO to develop an open source pharma consortium [44,50]. They have also created three fellowship programs through private donor funding which has contributed to the training of over 50 new scientists [50].

Implementation Considerations

OSDD is funded by a US$35 million grant from the Government of India [49]. Funding covers equipment and material costs at the partner institutions and the salaries of a few key contributors [51]. Estimating the cost-savings of this approach is difficult due to the complex and continuing nature of these projects; however, leaders in the field anticipate that the approach will be positive for R&D efficiency and costs [52]. The open source drug discovery approach should be appealing to government funders given the added benefits of transparency, as well as faster and more cost-effective deliverables using volunteer labour [45]. Additionally, governments may foresee benefits from contributing to the training of future scientists [44], and generating infrastructure that could assist in globally coordinated responses for future disease outbreaks. Although funding is required to establish a new open source project, the introduction of user fees has been suggested as a means of financial sustainability [40] (see Web Appendix for additional information on funder motivations and financial sustainability).

OSDD may provide increased efficiency of knowledge generation and dissemination, and reduced costs and wasteful duplication of research. However, its main challenges are a reliance on the goodwill of participants [41], its limited application in the R&D pipeline, a need for collaboration with PDPs, and the fact that pharmaceutical companies may not universally embrace such change [52].

Canada is a global leader in government-funded R&D and has the eighth largest pharmaceutical market in the world [53–55]. With its commitment to R&D and strong pharmaceutical industry, Canada is well-positioned to be a leader in open source drug discovery, and would benefit from measures
that increase the efficacy of its current R&D commitments. Attention to antibiotic resistance aligns with Canada’s G7 commitments to addressing this global health threat [56].

CASE STUDY 4: DRUGS FOR NEGLECTED DISEASES INITIATIVE MODEL

According to WHO, Neglected Tropical Diseases (NTDs) affect more than 1 billion people worldwide [57]. Of the 850 new therapeutic products approved between 2000 and 2011, only four percent were directed towards neglected diseases [58]. PDPs have emerged in the last decade in order to address the burden of NTD on developing countries [12]. PDPs are non-profit initiatives created to address the lack of commercial incentives to undertake research and development (R&D) for vaccines, diagnostics, and drugs [59]. They function as public private partnerships, and they specifically focus on the health technology development [60].

PDPs are able to develop effective, affordable, and accessible products by coordinating the resources and utilizing the infrastructure of particular partners at various stages of the R&D process [61]. PDPs perform a standard R&D process for drugs and develop programs ranging from clinical research platforms to licensure [60]. The same model is applied to each PDP with particularities accorded to accommodate different areas of expertise. PDPs undertake R&D for neglected diseases; they create disease project portfolios; they manage restricted and unrestricted funds received from private and public donors which are allocated for promising projects [62]; establish management policies concerning regulatory systems, manufacturing, marketing, and intellectual property [60]; and work with academics, research centers, the pharmaceutical industry, multilateral agencies, governments, philanthropic organizations, and regulatory bodies [63] (see Web Appendix for further details on the PDP model).

Product Development Partnership Model

Established in 2003, DNDi aims to develop new drugs, or new formulations of existing drugs, for seven neglected diseases [64]. DNDi embraces a patient centered, needs-driven approach, with the objective of improving access to knowledge and products. DNDi also establishes financial and scientific independence, and collaborates with partners including those from endemic countries. DNDi’s efforts have led to the development of a large portfolio based on short and long-term strategies that focus on the optimization of existing drugs and the development of new treatments [65].

The portfolio has five types of projects that cover different stages of the R&D process. These projects focus on the delivery of new treatments developed from compounds with known antimicrobial activities (from lead optimization or preclinical development). New indications for existing treatments (from therapeutic switching) are also being explored.
Efforts center on combinations of existing drugs adapted to field conditions and patients. New treatments are being developed from novel compounds (from screening, lead optimization, or licensing), and extension of existing treatments and completion of regulatory dossiers in new countries [66]. DNDi has designed a “gold standard” of licensing terms. As per its IP policy, R&D contracts are often made with public sector entities or partners who share its vision [67]. The greatest challenges reported have been the access to the compound libraries to identify new hits, the complex use of diagnostic and therapeutic tools and the harmonization of regulatory mechanism and new incentives [68] (see Web Appendix for the DNDi model). The DNDi case study serves the dual purpose of introducing a potential partnership opportunity, and illustrating the functioning and utility of the PDP as a model for potential implementation.

**Performance Indicators**

The PDPs address the lack of new treatments for neglected infectious diseases by revitalizing the discovery and development of the drug landscape. After ten years, DNDi has twelve new chemical entities (NCE) in the pipeline, six treatments delivered, and 25 clinical studies from phase I to IV conducted [68]. It has succeeded combining existing drugs to develop new treatments. This approach has improved safety and reduced treatment duration. Developing combination therapies is where the market-driven pharmaceutical model has failed because of the absence of profit [68]. Providing measures of health impacts is challenging given the poor quality of the data available as many PDPs are still developing [62].

**Implementation Considerations**

A PDP is a cost-effective model. The increase in neglected disease R&D funding for PDPs is an indicator of the efficiency of this mechanism [59]. This can be verified as DNDi funding has increased from €21.267 in 2009 to €31.242 in 2013 [62]. DNDi estimates the costs associated with developing new chemical entities to range between €100 million and €150 million, which is far lower than the billion dollar estimates asserted by the pharmaceutical industry [67].

Financial sustainability is a challenge for DNDi, the development of new treatments can take up to ten years; however most donors typically commit to short, two-five year investments terms. In response to this problem, DNDi has diversified its fundraising strategies and projects to reduce and share the financial risk among donors [62].

WHO and DNDi are currently exploring the PDP model to develop new antibiotic treatments to address antimicrobial resistance by combining or reformulating existing antibiotics [69]. The first expert meeting will be held in Germany in the next few years [70]. Canada could similarly capitalize on a PDP model for the innovation and production of affordable new treatments to address urgent needs and technologically risky R&D projects. Canada has one of the most comprehensive biopharmaceutical industry pipeline of products, and can bring together myriad public and the private sector players [71]. Canada could also potentially collaborate with DNDi; Canada’s scientific and technical expertise in R&D, in conjunction with Canada’s access to compound libraries, would benefit DNDi’s project portfolio.

**CASE STUDY 5: BULK PURCHASING SCHEMES TO IMPROVE AFFORDABILITY**

Government expenditures on prescription drugs comprise the second largest health-spending category and occupy approximately 13.4% of total health costs. In 2014, total drug spending in Canada was an estimated $33.9 billion, or $955 per person [72]. Undisputedly, pharmaceutical products are crucial components of modern healthcare [73]. New and more potent methods of subsidizing and regulating drug costs must be implemented to ensure proper access and affordability.
The Patchwork: A Residual Model of Social Welfare

Prescription drugs are not included in the services covered by Canada’s Medicare system; rather, multiple players, in a system commonly referred to as a “patchwork,” are involved in the financing of prescribed drugs [74]. Approximately 34.5% of pharmaceuticals are funded by private sector insurers; 22.2% of drug costs are paid out of pocket by individuals; and 41.6% of pharmaceutical expenses are covered by the federal, provincial, and territorial governments through a variety of different programs [75]. The federal government provides drug coverage for First Nations and Inuit, the Royal Canadian Mounted Police, active and retired military personnel, federal inmates, and refugee protection claimants [76]. Provincial and territorial governments, in accordance with the Canada Health Act, 1984, are required to provide universal coverage for medically necessary hospital and physician services [77]. As a result, all thirteen provinces and territories have developed independent public drug insurance programs under different eligibility cost sharing arrangements [77]. The lack of national standard has contributed to excessive spending and interprovincial disparities in public drug coverage [77].

Concerns over Canadians falling through the gaps of the current drug benefits scheme has led to repeated recommendations for the federal and provincial governments to adopt national ‘pharmacare’ standards. Since 1958, the federal government has contemplated strategies to control drug prices [73]. In 1964, the Royal Commission on Health Services and, in 1997, the National Forum on Health recommended that Canada implement a universal, public pharmacare programme [74]. Despite these calls for universal drug coverage, federal legislation has yet to be enacted [74]. Recently, the federal government and the provincial and territorial governments have united to capitalize on their combined purchasing power in an effort to lower drug expenditures. This case study seeks to explore the utility and effectiveness of bulk-purchasing, and alternative state, bulk-buying models.

Pan-Canadian Pricing Alliance & Bulk Purchasing

Bulk purchasing is a strategy that utilizes multiple purchasers to increase the volumes of drugs purchased to negotiate lower unit prices [78]. Bulk purchasing is currently practiced by the pan-Canadian Pricing Alliance (pCPA). The pCPA is a federal, provincial, and territorial initiative that capitalizes on the combined purchasing power of public drug plans across multiple jurisdictions to increase access to drug treatment options; lower drug costs; achieve consistent pricing; and improve the consistency of coverage criteria across the country [79]. Currently, the pCPA is seeking options for the development of a permanent mechanism or model to achieving better value in purchasing generic drugs.

The Australian Model

The Australian government employs its single drug purchasing system, or monopolistic purchasing strength, to achieve lower drug prices relative to those paid internationally. The Pharmaceutical Benefits Scheme (PBS), governed by the National Health Act, 1953, provides subsidized medications to patients [80]. The PBS acts both as an insurer and as a sole purchaser, negotiating prices for pharmaceuticals.
from suppliers. New medicines are added to the PBS on the recommendation of the Pharmaceutical Benefits Advisory Committee (PBAC), an expert advisory panel. The PBAC is responsible for providing advice to the Minister of the Department of Health and Ageing regarding which drugs to include on the Schedule of Pharmaceutical Benefits (SPB), a reimbursable drug list. The PBAC also informs the Pharmaceutical Benefits Pricing Authority (PBPA) of a drug’s comparability with existing alternative therapies and its cost-effectiveness [81]. Because listing under the PBS provides a significant marketing boost, the government is in a strong position to negotiate [80].

Performance Indicators

Although Australian expenditures on generic medicines are on the rise, Australia has historically spent, and continues to spend significantly less on pharmaceuticals than the majority of its comparator countries [82]; in 2014, 0.7% of Australia’s GDP was spent on medicines, which is well below the OECD average of 0.8% [83]. Mandatory pricing disclosure arrangements, which require manufacturers to reveal the actual prices they charge for medicines, has contributed to reduce drug expenditures [84]. Agreements made between industry and governments in 2007 will have contributed to approximately $20 billion in savings by 2017-18 [83]. Despite the PBS’s projected savings, expenditures are anticipated to continue to rise with nominal growth of approximately 5% per year projected to 2023-24 [84].

Implementation Considerations

Australia’s PBS is particularly viable to Canada because of the federal, legal, political, geographic, and economic similarities of the two nations [85]. Further, both the pCPA and the PBS are publicly funded models that favour single drug approval mechanisms. The Trans-Pacific Partnership (TPP) could limit the cost-effectiveness of the PBS, particularly due to new protections on biologic medicines [86].

Recommendation

Bulk-purchasing is an effective mechanism for exercising buyer market power and driving down prices [87]. Using this strategy, the pCPA has completed more than 89 negotiations on brand-name drugs and achieved price reductions on 14 generic drugs, resulting in combined savings of more than $490 million annually [88]. While bulk purchasing saves taxpayers money, bulk purchasing does not always meet the dual objectives of enhancing patient care while simultaneously cutting health care costs. At the national level, governments run the risk of inadvertently raising non-pharmaceutical health costs and limiting patient access to optimal medicines [87]. Bulk purchasing can also lead to a centralization in manufacturing and distribution, which ultimately impairs drug supply and patient care. Because Canadian jurisdictions are already in the midst of supply shortages for a number of drugs, a bulk purchasing scheme could potentially exacerbate this problem [89].

Although bulk purchasing is an appropriate step towards improving affordability, ultimately, a national pharmacare programme is the ultimate model for “bulk purchasing,” as it is able to achieve the best discounts from drug companies through a competitive bidding process. Canadian Minister of Health Jane Philpott suggested this possibility when she stated: “Our government is committed to improving the affordability of necessary prescription medication,” and “remain[s] open to exploring further ways we can collaborate with the provinces and territories to do so” [90]. Exploring innovative alternative pharmacare models, like the PBS, should be a priority area for future government exploration.

INTEGRATING THE CASE STUDY

The five case studies presented above demonstrate alternative models for pharmaceutical development and delivery in order to improve access to medicines. While the emphasis has been on drug development, this model is also relevant to the development of new vaccines, diagnostic tools, and
other health technologies. Figure 6 demonstrates the revised framework.

The case studies began with the Innovative Medicines Initiative (IMI) and the International Finance Facility for Immunization (IFFIm) as alternative models for financing. The IMI reflects one model for generating new funding for R&D activities through government and industry partnerships, while IFFIm has created a model for enhancing the efficacy of financial commitments through global financial markets. IFFIm's model, although developed for Gavi's vaccine programme, could be applied to commitments in many areas of global health, including R&D funding models such as the IMI. The next case study explored one of the first stages of drug development, the discovery phase. Open Source Drug Discovery (OSDD) was introduced as a collaborative development model for the quick and cheap generation of new R&D for drugs that do not adequately respond to current market incentives, including antibiotics. OSDD is best suited for the discovery stage and would benefit from a Product Development Partnership (PDP). The PDP model was demonstrated through the Drugs for Neglected Diseases Initiative (DNDi) case study, which was highlighted for its capacity to bring new drugs through the discovery stage to the market with a patient-centered focus. PDPs are able to incorporate collaborative funding and discovery approaches such as the IMI and OSDD models. Again, IFFIm could be used as a model to enhance donor commitments to either OSDD or PDPs. While the four market-level models would all contribute to bringing new drugs to the market at more affordable prices than traditional drug development, patient-level interventions are still needed to ensure that all medicines are affordable for all people. The final case study presented Australia's Pharmaceutical Benefits Scheme (PBS) as a potential model for improving bulk purchasing in Canada. More broadly, this model also signified the need for national pharmaceutical coverage. Together these case studies presented several alternative models of drug development and delivery capable of being integrated to improve the availability and affordability of medicines.
APPLICATIONS FOR CANADA

Globally, Canada is already one of the top five countries for government-funded R&D [54], and in 2014 the Federal Budget committed $1.5 billion over ten years to a long-term, strategic vision for research and innovation in Canada [55]. Canada also has the eighth largest pharmaceutical market in the world [53]. With its commitment to R&D and strong pharmaceutical industry, Canada is well-positioned to be a leader in drug development, and would benefit from measures that increase the efficacy of its current R&D commitments. Furthermore, Canada had the third highest drug prices in 2014, and the highest growth rate in drug expenditures (184.4%) over the past twelve years, among comparator countries [91]. Consequently, nearly one-quarter of all Canadian homes are unable to afford prescribed drugs [92]. Evidently, Canada needs to develop a strategy to lower the cost of drugs and expand public funding at the federal, provincial, and territorial level.

<table>
<thead>
<tr>
<th>International Partnership with Organisation</th>
<th>Development Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Innovative Medicines Initiative (IMI)</td>
<td>Not Recommended for Future Exploration</td>
</tr>
<tr>
<td>International Finance Facility for Immunisation (IFFIm)</td>
<td>Priority Area for Future Exploration</td>
</tr>
<tr>
<td>India’s Open Source Drug Discovery (OSDD)</td>
<td>Not Recommended for Future Exploration</td>
</tr>
<tr>
<td>Drugs for Neglected Diseases Initiative (DNDi)</td>
<td>Area for Future Exploration</td>
</tr>
<tr>
<td>Australia’s Pharmaceutical Benefits Scheme (PBS)</td>
<td>Not Applicable</td>
</tr>
</tbody>
</table>

Figure 7 categorizes recommendations for future exploration. The reviewed market-level models present possible international partnership opportunities for the Canadian government. IMI’s European-centered mandate and OSDD’s Indian-focused operations make both organizations less suitable partners. DNDi presents opportunities for the Canadian government to improve global access to medicines for neglected diseases and may make a valuable new partnership. However, IFFIm is the most suitable partnership for exploration. Given Canada’s current role as an active Gavi funder, IFFIm may provide a way for Canada to improve its current financial commitments to global vaccination programmes.

Lastly, each case study provides a possible alternative model for exploration at either the domestic or international level. IMI, criticized for a lack of transparency and being driven by pharmaceutical interests, does not appear to be an ideal model for improving access to medicines. The IMI model directs government financing to a research agenda driven by the interests of pharmaceutical companies. In turn, the IMI
model may not promote the affordability of medicines, or address pressing global health needs such as antibiotic R&D. IFFIm offers a novel mechanism for improving the efficiency of global health aid by engaging with financial markets to shift long-term development assistance commitments into readily available cash. However, engagement with financial markets that have experienced instability in recent decades must be done with great caution. Similarly, OSDD offers a novel mechanism for driving R&D in high-priority global health areas, such as antibiotics. Models of open source development are garnering increased global attention, and while the model has been successful in software development, a widespread global application to drug discovery is still needed. Both the IFFIm and OSDD models are worth future consideration by the Canadian government regarding operational logistics and cost-benefit analyses of implementation. At the market-level, PDPs, such as the DNDi model, may be the most valuable model for the Canadian government to explore. PDPs have the capacity to incorporate collaborative funding and development models, and can be tailored to meet both domestic and international health priorities. Finally, at the patient-level, exploring Australia’s PBS may assist in finding a model that improves the affordability of pharmaceuticals in Canada. While market-driven strategies, such as those described above, may improve the availability and affordability of pharmaceuticals entering the market, interventions at the patient-level are required in order to secure equitable access to medicines for all.

Key Messages

1. To improve access to essential medicines, Canada should explore international initiatives and consider alternative models that, at the market level, produce new drugs at more affordable prices, and, at the patient level, increase the affordability of pharmaceuticals.

2. Canada’s burgeoning pharmaceutical industry and demonstrated commitment to R&D would benefit from initiatives that increase the effectiveness of its current R&D investments.

3. Improved cooperation between the federal, provincial, and territorial governments reflect a shift in the political climate that may allow new opportunities for bulk-purchasing initiatives and beyond.

4. Canada plays a significant role in the international effort to improve global health, and in order to bolster its impact abroad, partnerships with IFFIm and DNDi should be seriously considered.

5. An integrated health model that contemplates the complex and unresolved dialogue surrounding access to medicines is best suited to appreciate the complexity of the global health system.
REFERENCES


29. IFFIm. IFFIm Overview [Internet]. IFFIm Support. Gavi Vaccine Alliance. [cited 2016 Jan 22]. Available from: http://www.iffim.org/about/overview/


47. Maurer S. The right tool(s): designing cost-effective strategies for neglected disease research [Internet]. Goldman School of Public Policy; 2005 [cited 2016 Mar 8]. Available from: http://www.who.int/intellectualproperty/studies/S.Maurer.pdf

48. Rydzewski RM. Real world drug discovery: a chemist’s guide to biotech and pharmaceutical research [Internet]. Oxford, UK: Elsevier; 2008 [cited 2016 Mar 9]. Available from: https://books.google.ca/books?hl=en&lr=&id=9ELvBMCyKKwC&oi=fnd&pg=PP2&dq=Real+world+drug+discovery%3A+a+chemist%27s+guide+to+biotech+and+pharmaceutical+research&ots=XRHZU5-44K0&sig=YSPNGdC2bcsunmNgOGh4Rs6_j0y0

50. Open Source Drug Discovery. OSDD foundation day: brief report [Internet]. 2014 [cited 2016 Mar 8]. Available from: https://docs.google.com/viewer?a=v&pid=sites&srcid=b3NkZCSuZXR8b3NkZGSld3Zicnlzb258Z3g6MzVhNmMzMjJjNTg0NDJjMw


54. Committee on Development and Intellectual Property. Alternatives to the patent system that are used to support R&D efforts, including both push and pull mechanisms, with a special focus on innovation-inducement prizes and open source development models [Internet]. World Intellectual Property Organization; 2014 [cited 2016 Mar 8]. Available from: http://www.wipo.int/edocs/mdocs/mdocs/en/cdip_14/cdip_14_inf_12.pdf


104. MPP. About the MPP [Internet]. Med. Pat. Pool. date unknown. Available from: http://www.medicinespatentpool.org/about/


123. PATH. Path malaria vaccine initiative [Internet]. Available from: http://sites.path.org/mvi/


130. Gavi, the Vaccine Alliance. All about IFFIm [Internet]. Gavi, the Vaccine Alliance; 2015 [cited 2016 Mar 19]. Available from: http://www.gavi.org/About/Governance/GAVI-Board/Minutes/2015/10-June/Presentations/Technical-Briefing---Gavi-Finance-and-IFFIm/


132. Twentyman J. Linux tries not to be victim of its own success. Financ. Times [Internet]. 2008 Mar 19 [cited 2016 Mar 9]; Available from: http://www.ft.com/intl/cms/s/0/adb45b00-f1e0-11dc-9b45-0000779fd2ac.html#axzz42MmJLav4


Methodology

Search Strategy
We oriented our search around information available on the webpages of both state and non-state actors identified as key international players in improving access to medicines. Our state actors included Canada, the US, the UK, Australia, New Zealand, Norway, Sweden, Denmark, Finland, Iceland, the European Union (EU), and BRICS (Brazil, Russia, India, China, and South Africa). Non-state actors included the World Health Organization (WHO), Médecins Sans Frontières (MSF), the HIV/AIDS Legal Network, the Organization for Economic Cooperation and Development (OECD), the Pan-American Health Organization (PAHO), the Global Fund, the Global Alliance for Vaccines and Immunization (Gavi), and the United Nations Programme on HIV/AIDS (UNAIDS).

We began with these organizations and employed an adapted-snowball sampling approach, whereby new organizations were identified based on online information acquired from the original sample.

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action</td>
<td>Any relevant activity undertaken by such individual or organization</td>
</tr>
<tr>
<td>Actor</td>
<td>Any individual or organization participating in improving access to medicines</td>
</tr>
<tr>
<td>Campaigns</td>
<td>A series of actions or events meant to achieve a particular result, including fundraising and awareness campaigns</td>
</tr>
<tr>
<td>Collaborations</td>
<td>Joint efforts in a specified intellectual endeavor, including working groups, commissions, and committees</td>
</tr>
<tr>
<td>Declarations</td>
<td>International instruments which may be non-legally binding and aspirational, binding at international law, or originally non-binding, but gaining binding character as customary law</td>
</tr>
</tbody>
</table>
Data Extraction and Terminology
Our data review involved developing an extraction table based the actor-action dyads we identified. For each dyad, we recorded the type of actor, actor name, type of action, action name, the access to medicines area addressed, whether the action was proposed or implemented and when, as well as a brief description of the action's aim. Detailed summaries were subsequently developed for each dyad.
We assigned each dyad to one of seven areas of access to medicines: (1) research and development; (2) intellectual property rights and patents; (3) access to and delivery of treatment; (4) counterfeit and quality; (5) building domestic capacity; (6) improving global health aid; or (7) multidimensional, when applicable to more than one of the preceding categories.

Network Graphing
We used a network graphing technique with the assistance of NodeXL 2014 software. A graph is a collection of vertices (points), connected by edges (lines), which may be directed, implying a causal direction, or, as here, undirected, indicating a relationship. Within a graph, edges may overlap, and multiple edges may extend from a single vertex. We utilized network graphing as a data visualization tool, rather than as an analytic approach. The maps offered the benefit of drawing conclusions from a visual presentation of the results that could not otherwise be captured from a review of the summary table provided in the Web Appendix. These include the visualization of interconnectivity among different actors and actions within each map, and the varying integration levels between areas, which may highlight redundancies within the

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyad</td>
<td>Unique actor-action pairing</td>
</tr>
<tr>
<td>Financing</td>
<td>The provision of monies for third party activities</td>
</tr>
<tr>
<td>Frameworks</td>
<td>Products, often the result of a collaboration, intended to guide future actions and activities, including reference lists and electronic tools</td>
</tr>
<tr>
<td>Global Action Plans</td>
<td>Policy options to guide WHO member states’ efforts to reach international health targets</td>
</tr>
<tr>
<td>Legislation</td>
<td>Laws enforced by an official organ of a state or other organization</td>
</tr>
<tr>
<td>Programmes</td>
<td>Coordinated activities targeting the direct or indirect provision of products or services</td>
</tr>
</tbody>
</table>
system that could be addressed. Additionally, they provide a visualization of centrality, demonstrating which actors and actions play a central role in a specific area, and which actors or actions operate at the periphery and may benefit from additional support. Finally, the maps provide a powerful visual display of the gaps in actors and actions in certain areas of access to medicines.

**Access to Medicines Themes**

**Campaigns**

Campaigns developed to improve global access to medicines comprise a broad spectrum of strategies that promote awareness, raise funds, develop and disseminate research and information, and engage individuals, organizations, and countries. Some interesting online campaign initiatives include UNAIDS’ My World, a noteworthy enterprise that engages individuals through an online crowdsourcing platform, where people can prioritize global health issues and share ideas [93]. Other online campaigns include The Index, which is run by the United Nations and publicly recognizes pharmaceutical industries for their investments in access to medicines, providing corporations with a means to assess, monitor, and improve their own performance, as well as their public and investment profiles [94]. Most campaign initiatives are directed towards combating HIV/AIDS. In line with the 2015 Millennium Development Goals (MDGs), the UNAIDS Strategy prompts countries to set targets for universal access to HIV prevention, treatment, and support, and to halt and reverse the spread of HIV [95]. The MAC AIDS Fund, through the sale of lipstick, capitalizes on the star power and influence of celebrities to deliver HIV treatment and care for young people worldwide [96]. A number of campaigns focus on improving access to medicines through the promotion, funding, and dissemination of research. Doctors without Borders Canada (MSF), for example, focuses on stimulating research of new medicines for HIV as well as neglected diseases, such as tuberculosis (TB), sleeping sickness, kala azar, and Chagas disease [8]. Further, PAHO, via the Lancet, promotes a strategy for achieving universal access to health in Latin America [97]. UNAIDS also collaborates with the Lancet to provide data concerning HIV, scientific opportunities, and social progress [98].

**Financing**

Access to essential medicine is tied to availability and affordability issues, and requires that financial strategies promote sustainability. Both state and non-state actors employ particular techniques to increase access. Some of these strategies include, developing efficient procurement practices; maximum pricing policies and competition strategies; facilitating parallel imports; and the granting generics and compulsory licensing. Alternatively, states also provide access by offering to reimburse those who cannot pay, and they are broadening their efforts by looking beyond developing manufacturing capacity domestically with the view to promote the production of pharmaceuticals and vaccines abroad [99].

There are a considerable number of collaborations between states, intergovernmental organizations, and NGOs, often in the form of public-private partnerships. By harnessing their respective and collective strengths, these collaborations are creating innovative fund-raising opportunities, accelerating procurement and ensuring the quality of essential medicines. For example, EU member states reached a joint procurement agreement by incentivizing their pharma partners to reduce costs and increase access to biological products [100]. The PAHO Strategic Fund supports member states by managing supply systems and ensuring international quality standards [101]. The Stop TB Partnership heads a novel procurement mechanism known as the Global Drug Facility (GDF) that links demand for drugs to supply and monitoring, and outsources all services to collaborating partners on a competitive basis [9].

Partnerships, such as the Global Fund [102] the UNESCO-OPEC Fund [103], the Global Health Innovative Technology Fund (GHIT) [104], and the US President’s Malaria Initiative (PMI) [105], among numerous others, are finding ways to improve access to medicines by providing innovative, sustainable funding for medicines, diagnostics, and prevention of HIV/AIDS, TB, and malaria in developing countries. For example,
<table>
<thead>
<tr>
<th>Access to Medicine Thematic Areas by Action Type</th>
<th>Actor Types</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>State</td>
</tr>
<tr>
<td>Campaign</td>
<td>1</td>
</tr>
<tr>
<td>Intellectual Property Rights/Patents</td>
<td>1</td>
</tr>
<tr>
<td>Multidimensional</td>
<td>1</td>
</tr>
<tr>
<td>Research and Development</td>
<td>1</td>
</tr>
<tr>
<td>Treatment Access/Delivery</td>
<td>1</td>
</tr>
<tr>
<td>Collaboration</td>
<td>10</td>
</tr>
<tr>
<td>Counterfeit/Quality</td>
<td>3</td>
</tr>
<tr>
<td>Intellectual Property Rights/Patents</td>
<td>1</td>
</tr>
<tr>
<td>Multidimensional</td>
<td>3</td>
</tr>
<tr>
<td>Research and Development</td>
<td>6</td>
</tr>
<tr>
<td>Declaration</td>
<td>1</td>
</tr>
<tr>
<td>Multidimensional</td>
<td>1</td>
</tr>
<tr>
<td>Financing</td>
<td>14</td>
</tr>
<tr>
<td>Domestic Capacity</td>
<td>2</td>
</tr>
<tr>
<td>Intellectual Property Rights/Patents</td>
<td>2</td>
</tr>
<tr>
<td>Multidimensional</td>
<td>4</td>
</tr>
<tr>
<td>Research and Development</td>
<td>2</td>
</tr>
<tr>
<td>Treatment Access/Delivery</td>
<td>6</td>
</tr>
<tr>
<td>Framework</td>
<td>3</td>
</tr>
<tr>
<td>Counterfeit/Quality</td>
<td>1</td>
</tr>
<tr>
<td>Improving Global Health Aid</td>
<td>1</td>
</tr>
<tr>
<td>Treatment Access/Delivery</td>
<td>2</td>
</tr>
<tr>
<td>Global Action Plan</td>
<td>2</td>
</tr>
<tr>
<td>Multidimensional</td>
<td>1</td>
</tr>
<tr>
<td>Treatment Access/Delivery</td>
<td>1</td>
</tr>
<tr>
<td>Legislation</td>
<td>7</td>
</tr>
<tr>
<td>Counterfeit/Quality</td>
<td>1</td>
</tr>
<tr>
<td>Intellectual Property Rights/Patents</td>
<td>3</td>
</tr>
<tr>
<td>Multidimensional</td>
<td>1</td>
</tr>
<tr>
<td>Treatment Access/Delivery</td>
<td>3</td>
</tr>
<tr>
<td>Programme</td>
<td>4</td>
</tr>
<tr>
<td>Multidimensional</td>
<td>1</td>
</tr>
<tr>
<td>Research and Development</td>
<td>1</td>
</tr>
<tr>
<td>Treatment Access/Delivery</td>
<td>3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>39</strong></td>
</tr>
</tbody>
</table>
UNITAID [106] finances its initiatives through an international solidarity levy on airline tickets - a fee attached to all departing flights - currently collected in nine out of 29 member countries.

There are a host of public-private partnerships specifically designed to fund and carry out scientific research and development (R&D); their primary objectives are to find effective and affordable strategies to improve the health and health equity of LMIC populations. With the help of important partnerships, such as Gavi, states and NGOs are ensuring that production and delivery strategies are developed and updated through in-depth analysis and far-ranging consultations.

There are also examples of actions that target the restrictions imposed by intellectual property rights (IPR) and practices. While patent protection provides incentives for the R&D of new medicines, IPRs often work to prevent developing countries from producing or buying generics. The Medicines Patent Pool (MPP) [10] is an innovative mechanism offering a public health-driven business model that aims to lower the price of medicines and facilitate the development of better-adapted treatment through voluntary licensing and patent pooling. The Health Impact Fund (HIF) [100] proposes a wholesale restructuring of the traditional patent protection system by offering patent-holders financial rewards when they opt to register their new medicines, or new uses of existing medicines with the Fund. By registering, a patent-holder agrees to distribute its medicine globally at a cost. In return, the firm receives an annual reward based on its measurable contribution to reducing the global burden of disease.

Frameworks

Often a collaborative effort, frameworks are undertaken by both state and non-state actors. And in the context of improving global access to medicines, frameworks are instrumental in guiding future global initiatives in the financing and procurement of essential drugs. Every two years, the WHO updates Model Lists of core and complementary medicines that enable health authorities to optimise pharmaceutical resources. Both developed and developing governments refer to the WHO’s recommendations when deciding on health spending. Affiliated states are encouraged to prepare independent lists based on local priorities and needs; over 150 countries have taken part in this framework [107]. Similarly, the Equitable Access Initiative [108], driven by the Global Fund and Gavi, provides a new framework to best identify the needs and constraints surrounding equitable access to health, including medical technologies and medicines for countries transitioning from LMIC status. This framework classifies countries according to key components of equitable access, which could help define the approach taken by the Global Fund and other agencies in adopting both procurement and funding eligibility criteria [109].

State actors, such as the EU G10 Medicines Group and the United Kingdom’s (UK) Outcomes Framework, collaborate to pursue and achieve an array of international health objectives. The Outcomes Framework developed collaborative approaches to unify government departments and priorities on foreign policy, to improve both international aid and the UK’s population health outcomes. Specifically, the Outcomes Framework endeavours to collaborate with emerging economies to improve health by focusing on global health security, international development, and trade [10]. The EU’s G10 recommendations for action seek to improve the pharmaceutical market, stimulate and improve the European science base, and produce better information for patients [110].

Procurement initiatives encompass ongoing efforts directed at quality control by the WHO, while new efforts propose interesting online procurement platforms. Every year, international procurement agencies spend billions of dollars on medicines to distribute in resource-limited countries. The WHO’s Prequalification Program is a service that assesses the quality, safety, and efficacy of procured medical products. At the end of 2012, the WHO’s list of Prequalified Medicinal Products contained 316 medicines for priority diseases. Prequalification is intended to give these procurement agencies a wide range of quality medicines for bulk purchase [111]. With respect to the financial component of procurement,
the E-Marketplace, a proposed online procurement platform for commodities, has been described as an ‘Amazon.com for aid.’ The E-Marketplace would allow principal recipients, such as the Global Fund, to purchase various medicines and health related commodities; thus, decreasing long delays and increasing supplier and pricing transparency [112].

**Legislation**

Legislation informs and directs the initiatives of many state and some non-state actors. The statutory instruments employed are multifarious in their objectives, but many aim to reform intellectual property and patent laws; develop a method of administering universal health care; and combat counterfeit drug trafficking. The EU has adopted legislation concerning compulsory licensing of patents relating to the manufacturing of pharmaceutical products for export to countries with serious public health issues [5]. The EU has also adopted legislation to encourage pharmaceutical companies to sell their medicines at lower prices in developing countries [113]. The Promotion and Protection of Investment Bill (“PPIB”) aims to review and terminate bilateral investment treaties (BITs), and free-trade agreements (FTAs) with EU members to protect health regulations and align the treatment of foreign investments in South Africa [114].

Canada’s Access to Medicines Regime (CAMR) provides a framework through which some of the world’s poorest nations are able to import less expensive generic versions of patented drugs and medical devices. Established in 2004, CAMR is one part of Canada’s broader strategy to assist countries in their struggle against HIV/AIDS, TB, malaria, and other diseases. In 2008-09, CAMR was used to make two shipments of a patented antiretroviral medication to Rwanda. Due to bureaucratic and economic obstacles, it has not been used since. However, there may still be a place for CAMR in Canada’s future with respect to the potential import of biologics rather than generics [115].

The Chinese government aims to achieve universal healthcare coverage by 2020. By creating two comprehensive insurance plans, they have already increased the population’s access to medicine and health care. In 2006, only 40% of the population had health care coverage; and by 2011, almost 90% of the population had health insurance [116].

Interestingly, in 2011, the UN Security Council implemented Resolution 1983, which combats the spread of HIV by ensuring social stability. The resolution calls for efforts to increase communication between member states; education and best practice policy for prevention; and international cooperation through peacekeeping missions and training. Additionally, it seeks to address and combat gender inequality and gender-based violence; encouraging prevention and treatment [117].

Through separate initiatives, both the UN and Canada are combating the trafficking and countering of fraudulent medicines. The UN Office of Drugs and Crime, via Resolution 20/6, urges relevant international and regional institutions to strengthen and implement mechanisms to prevent fraudulent drug trafficking and strengthen international cooperation [118].

**Programmes**

Programmes are group initiatives that aim to either directly or indirectly influence the development, procurement, and distribution of essential medical products and services. Notable programmes directed towards HIV/AIDS relief include the President’s Emergency Plan for AIDS relief (PEPFAR), the Global AIDS Program (GAP), and the International Partnership for Microbes. PEPFAR is the foundation of the US President’s Global Health Initiative that specifically focuses on improving the health of women, children, and newborns. It endeavours to save the greatest number of lives possible by supporting countries as they work to improve their population’s health [12]. GAP partners with the American government to help implement PEPFAR. GAP helps resource-constrained countries prevent HIV infection, improve treatment and support for people living with HIV, and build capacity and infrastructure to address the global HIV/AIDS pandemic [31]. Finally, the International Partnership for Microbicides aims to prevent the spread of HIV by developing safe and effective microbicides [119].
There are also a number of programmes designed to address TB and malaria. The Drugs for Neglected Disease Initiative is a collaborative non-profit programme developing new treatments and new formulations of existing drugs for individuals suffering from the most neglected communicable diseases [120]. The Vaccine Fund, an initiative of the Global Alliance for TB Drug Development, spurs the global search for newer, simpler, faster-acting TB drug regimens [14]. UNITAID's Medicines for Malaria Venture is a leading product development partnership responsible for the R&D of antimalarial drugs. It aims to reduce the burden and eventually eradicate the presence of malaria through the discovery and development of new, effective and affordable antimalarial drugs [31].

Two programmes direct their efforts towards the use, safety, and development of drugs. The EC/ACP/WHO Partnership on Pharmaceutical Policies strives to improve population health in African Caribbean and Pacific Group of States (ACP) by increasing the availability and affordability of essential medicines and ensuring acceptable standards on drug quality [121]. The Innovative Medicines Initiative (IMI) seeks to improve health by accelerating the development of, and patient access to next generation vaccines and antibiotics [122].

Several programmes concentrate on global distribution, funding, or development of vaccines. Gavi provides the poorest nations with select vaccines, financial support, and safe-injection equipment. To show support for Gavi’s immunization programme, Canada has promised US$ 500 million by 2014 (53). The Vaccine Fund provides the poorest nations with select vaccines, financial support to strengthen immunization systems and safe-injection equipment [123]. And the International AIDS Vaccine Initiative (IAVI) is a global not-for-profit organization that researches, designs, and develops safe, effective, accessible, and preventive HIV vaccines for global use [124]. Lastly, the PATH Malaria Vaccine Initiative (MVI) is working to accelerate the development and use of malaria vaccines [123].

Global Action Plans
Global action plans typically guide WHO member states in achieving international health targets. In 2014, the WHO proposed a Global Action Plan to combat antimicrobial resistance [11]. The plan’s objective is to ensure the continued treatment and prevention of an ever-increasing range of infections caused by bacteria, parasites, viruses, and fungi. In 2012, WHO implemented another global initiative, the Global Vaccine Action Plan (GVAP). GVAP aims to increase access to existing vaccines for people worldwide, and to accelerate control of vaccine-preventable diseases, with polio eradication as the first milestone. Endorsed by 194 members of the WHA, GVAP proposes a framework that aims to save millions of lives by 2020 [124]. Global action plans assist state actors in achieving international health targets. The Global Action Plan and the GVAP are examples of recent initiatives aiming to combat antimicrobial resistance and increase access to existing vaccines for people worldwide. Canada is presently involved in these international initiatives.

Collaborations
Collaborations are joint efforts undertaken to approach intellectual endeavours. Most collaborations center on R&D initiatives that aim to promote research and/or education in the pursuit of improved international health, intellectual property laws, and response to global threats and epidemics.