Therapeutics for Emerging Infections with Pandemic Potential: Pipeline Portfolio Review and Cost Model

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
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ABSTRACT

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Abstract

Background: Since December 2015, the World Health Organization (WHO) Research and Development (R&D) Blueprint for Action to Prevent Epidemics[1] has maintained a list of 10 priority pathogens that have a high epidemic and pandemic potential and no or few medical countermeasures (MCMs, i.e., vaccines, diagnostics, and therapeutics). Barriers to facilitating R&D for these MCMs include lack of information on what candidate MCMs are currently in the pipeline, the estimated costs to advance this portfolio of candidates through the pipeline and the anticipated product launches. This study aimed to help close these information gaps, focusing specifically on the pipeline of therapeutics for the 10 "Blueprint diseases". Methods: We conducted a pipeline portfolio review to summarize which candidate therapeutics against the 10 priority diseases are currently in the pipeline, and at what development phase. Based on this pipeline, we then estimated the costs of moving these candidates through the pipeline, using a modified version of a financial modeling tool called the Portfolio to Impact (P2I) model. The model also estimates likely product launches. Based on the current pipeline, there would be no launches of therapeutics for several of the 10 diseases; we used the model to estimate the additional costs to launch these "missing" products. Results: The pipeline portfolio review identified 78 candidate therapeutics for the 10 Blueprint diseases as of December 3rd, 2018. The pipeline is dominated by Zika and Ebola, whereas the other Blueprint pathogens have very few candidates. The P2I model

estimates that it would cost $1.76 billion to move these current candidates through the pipeline from 2019 to 2030, which would lead to an estimated 8.78 cumulative product launches. These launches would be dominated by simple biologics (n=2.30) and simple repurposed drugs (n=4.92). The three diseases that are likely to have the most product launches are Ebola (n=3.21), Zika (n=2.91), and Rift Valley Fever [RVF] (n=1.42). For the other seven Blueprint diseases, the model suggested there would be no launches of therapeutics. We estimated that it would cost an additional $0.64 billion to $1.46 billion dollars to launch these "missing" therapeutics (i.e., one therapeutic for each of these seven diseases), depending on the complexity of the product type. Conclusions: Our study found that while the current pipeline is likely to lead to launches of therapeutics for three of the Blueprint diseases—Ebola, Zika, and RVF—it is unlikely that there would be launches for the other diseases. We hope our results will help to mobilize additional financing and to inform new funding mechanisms, which are urgently needed for emergency response and preparedness against the highest threat diseases. We also hope that the study results will help identify where the pipeline has gaps, so that funding can be better directed to areas of greatest need.

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Acknowledgements

This study is part of a project led by Dr. Gavin Yamey at Duke, on the financing of global public goods for health, funded through a grant from the Bill & Melinda Gates Foundation to the Center for Policy Impact in Global Health (CPIGH) based in the Duke Global Health Institute (DGHI).

I want to express my deepest gratitude to my supervisor, Dr. Gavin Yamey, for his valuable patience and constructive guidance in every step of this study. His vigorous academic attitude and unextinguished enthusiasm to global health policy enlighten my future path. I`m very thankful to my sharp team, Shashika Bandara, Alexander Gunn, and Eugene Wang, who provided support and helped this thesis come to fruition. I would also like to recognize my committees, Dr. Chris Woods and Dr. L Gayani Tillekeratne. Without their valuable feedback and commitment, this thesis could not have been completed. Last but not least, I would like to thank DGHI, my family, and my country, for always supporting me with resources and freedom to learn to become an independent and responsible adult.

1. Introduction

The unprecedented outbreak of Ebola virus disease in West Africa from 2014-2016 showed the poor state of outbreak preparedness among the global public health community. The 2014-2016 epidemic crisis caused 28,603 reported cases with 11,301 deaths from Ebola up to February 14, 2016 in Guinea, Liberia and Sierra Leone[2]. Ebola virus was first identified in 1976, but to date there have been no licensed treatments proven to neutralize the virus[3] . The scale of the West African outbreak prompted public, private and multilateral health organizations (including the WHO, Médecins sans Frontières and Partners in Health) to treat patients using previously untested, unregistered medical products, and the WHO issued guidance on the ethics of such use[4,5,6]. With the increasing number and variety of global infectious outbreaks from 1980 to 2013[7] and the detrimental public health, economic, and social impacts of epidemics, there is an urgent need to develop better tools (particularly therapeutics, diagnostics, and vaccines) for epidemic and pandemic preparedness and response.

One essential way of facilitating R&D for epidemic and pandemic preparedness is to estimate the "price tag" for developing global health technologies (especially medicines, vaccines, and diagnostics), which are also known as medical countermeasures (MCMs). The WHO R&D Blueprint for Action to Prevent Epidemics "is a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics."[8] Since December 2015, the Blueprint has maintained a list

of priority pathogens that have a high epidemic and pandemic potential and no or few MCMs; there are currently 10 diseases on the list (Table 1[1]).

Table 1: List of Blueprint Priority Diseases[1]

- Crimean-Congo haemorrhagic fever (CCHF)
- Ebola virus disease
- Marburg virus disease
- Lassa fever
- Middle East respiratory syndrome coronavirus (MERS-CoV)
- Severe Acute Respiratory Syndrome (SARS)
- Nipah
- Henipaviral diseases
- Rift Valley fever (RVF)
- Zika

To the best of our knowledge, we know of two previously published estimates of the price tag to develop MCMs for epidemic and pandemic preparedness—one published by the WHO and the other by the Commission on a Global Health Risk Framework for the Future.

- *The WHO estimate.* A May 2016 report published by the WHO, as part of the R&D Blueprint deliberations, estimated the funding needs to develop a portfolio of different MCMs (e.g., vaccines diagnostics, repurposed drugs) for each Blueprint pathogen. The report concluded that "up to $1.17B would have to be invested for each pathogen, although R&D could be considerably cheaper, if built on existing technologies."[8] This estimate included development costs from preclinical to the end of phase I trials.

- *The estimate by the Commission on a Global Health Risk Framework for the Future*[9]. This Commission was convened by the National Academy of Medicine to bring together different experts from multiple sectors to devise a pandemic preparedness plan. The Commission recommended targeting incremental spending of $ 1 billion per year for at least 15 years for the development and production of a range of MCMs, including diagnostics, vaccines, drugs, and equipment. Based on this level of investment, if a known pathogen causes an outbreak, scientists would have already conducted most of the necessary preliminary research, and some of the products would have been delivered promptly into clinical testing, regulatory approval, production and deployment. This $1 billion per year estimate is roughly similar to "a small–medium pharmaceutical company's R&D portfolio of promising drugs and vaccines for key target diseases that are in various stages of development."[9]

However, these two estimates assume that the pipeline is empty—that is, they estimate the possible costs to develop MCMs "from scratch". In reality, the pipeline is not empty and various candidates for several of the 10 Blueprint priority pathogens are now under development. With this in mind, and to help mobilize additional financing to develop MCMs for infectious diseases with epidemic/pandemic potential, it would be valuable for R&D funders to have up-to-date information on:

- which candidate MCMs are currently in the pipeline and at what development phase;
- the estimated costs to advance this current portfolio of candidates to production;
- the anticipated product launches that would result from such acceleration;
- the critical, highly needed products that would still be "missing" at the end of this process.

This information would also help to inform new and innovative funding mechanisms, which are urgently needed for emergency response and preparedness against the highest threat diseases[11]. It would help to show where the pipeline is most robust and where it has gaps, which in turn can help to direct funding to areas of greatest need.

Our study aims to help narrow these information gaps. The study focuses specifically on therapeutics. It excludes vaccines and diagnostics, because the Coalition for Epidemic Preparedness Innovations (CEPI), which develops pandemic vaccines, has published a parallel study that focuses on vaccines,[12] and it excludes diagnostics because the Geneva-based product development partnership FIND is currently conducting a pipeline portfolio review and cost model on diagnostics.

We conducted a pipeline portfolio review to identify which candidate therapeutics against the 10 priority Blueprint diseases are currently in the pipeline, and

at what development phase. Based on this pipeline, we then estimated the costs of moving these candidates through the pipeline, using a modified version of a financial modeling tool called the Portfolio-to-Impact model (P2I model)[13]. The tool was developed by TDR, the Special Programme for Research and Training in Tropical Diseases. The financial model is based on assumptions about the cost, probability of success, and time spent per phase for each different type of MCM (known as an "archetype", e.g., repurposed drugs, new chemical entities (NCEs), biologics). The model also estimates likely product launches.

STUDY AIMS

AIM 1: To conduct a product portfolio review for therapeutic candidates against 10 priority emerging infectious diseases.

AIM 2: To estimate the overall cost of moving current candidates to the end of phase III trials and the likely product launches.

AIM 3: To estimate which critical MCMs will still be "missing" at the end of the pipeline and their likely development costs.

2. Methods

This study involves a pipeline portfolio review and then a financial modeling exercise. In the portfolio review, we conducted a review of the current pipeline to identify which therapeutics are under development for the 10 Blueprint priority diseases, and at what development phase. We then classified these candidates by each different type of MCM (known as an "archetype", e.g., repurposed drug, NCEs, biologic), level of complexity, and current stage of development. The reason for doing this classification is that the financial modeling tool that we used, an adapted version of the P2I model, is based on assumptions about the cost, probability of success, and cycle time per phase for each different archetype. To use this model, users must input the product development candidates according to their archetype, complexity level and development phase.

After identifying the candidates in the pipeline, for each disease and archetype, we then inputted the number of candidates that were in each phase of development into the P2I model. The model includes four phases: advanced preclinical, phase I, phase II, and phase III. We then ran the P2I model to estimate a) *output 1:* the costs to advance this current portfolio of candidates to launch, b) *output 2:* the anticipated product launches that would result from such advancement, c) *output 3:* which critical, highly needed products will still be "missing" at the end of this process, and d) *output 4:* the additional development costs to launch these "missing" products.

Overall, there were five methodological steps to this study: 1) identifying the candidate therapeutics in the current pipeline at four phases; 2) classifying each candidate therapeutic into its archetype (product type, i.e., repurposed drug, new chemical entity [NCE], or biologic) and complexity level (simple versus complex); 3) inputting the pipeline of therapeutic candidates into the P2I model; 4) estimating the costs of developing "missing" products; and 5) sensitivity analysis.

The study is based on publicly available data on therapeutic candidates that are currently in the pipeline. We collected data on the name of the candidate, the disease that it targets, and the phase of development. The study collected no patient data and was not human subjects research. For candidates that are in a clinical trial phase, the clinical trial registry may state the number of patients in the trial. Our proposed analysis of existing data was approved by the Duke University Campus Institutional Review Board (IRB) before the initiation of the study (approval was on March 14th, 2018).

2.1 Identifying the candidate therapeutics in the current pipeline at four stages

To identify therapeutic candidates in the pipeline targeting the 10 Blueprint priority diseases, we conducted a pipeline portfolio review comprised of two sequential processes: a literature search and a validation of the search results by technical experts.

2.1.1 Literature search

From May 28th, 2018 to October 17th, 2018, we collected data on the current therapeutic candidates under development for the 10 Blueprint priority diseases. We

included therapeutic candidates that are currently at four stages: 1) advanced preclinical; 2) phase l clinical trial; 3) phase II clinical trial; and 4) phase III clinical trial. The advanced preclinical stage is defined as the preclinical phase after lead optimization, which covers toxicology assessment, pharmacology, and pharmacokinetics/ pharmacodynamics (PK/PD)[11]. The advanced preclinical stage excludes early discovery (e.g., target identification and validation, assay development, etc.).

We collected data on the therapeutic candidates under development from multiple data sources. The most comprehensive source is the Citeline Pharmaprojects website, which was launched in 1980 and which contains information on medical products in the pipeline[14]. To supplement our search, we also gathered data from Clinicaltrails.gov, NIH Reporter, the International Clinical Trials Registry Platform (ICTRP), PubMed, and the WHO Observatory for R&D. We cross-referenced our results with data found on the websites of drug companies and product development partnerships (PDPs). Our search strategy was based on combining the names of the diseases with the terms [developer name], [candidate name], [development phase], [therapeutic], [therapy], [treatment], [intervention], and [assay]. Searches were not limited to any time frame, because there were relatively few records for the 10 Blueprint diseases identified through database searches (especially in comparison to the very large number of candidates under development for neglected tropical diseases[15]).

For the therapeutic candidates included in our initial pipeline, we extracted their information up to the end date of October 17th, 2018. We documented the candidate name, target disease, development phase, key developers, and search sources.

2.1.2 Validation process

In our initial search for therapeutic candidates, some candidates appeared to be listed under different names (e.g., ranpirnase, onconase and P-30 protein are all different names for the one candidate). In order to avoid double counting and to validate our results, we shared our initial pipeline with technical experts from Policy Cures Research[16] (PCR). PCR is a non-profit global health think tank providing research and strategic analysis related to global health R&D, including R&D for emerging infectious diseases. From October 18th to December 3rd, 2018, PCR reviewed and validated the pipeline, clarified information on each candidate's name, disease target, and development phase, and removed duplicate candidates.

Based on consultation with the developers of the P2I tool at TDR, we decided to keep duplicate candidates and input them into the P2I model under one of the following three circumstances:

a) the same candidate is given via different routes of administration (e.g., oral, topical, sub-cutaneous , intra-muscular). Each of these development pathways are distinct, so we erred on the side of being inclusive.

b) the same candidate is given for different diseases (e.g., intravenous ranpirnase is listed as being under development for both Ebola and SARS). Again, these are distinct product development pathways.

c) the description of the same drug produced by different companies is very generic (e.g., monoclonal antibodies for Ebola, Company X). When these companies were producing relevant candidates with simply synonyms, we erred on the side of assuming that these are different candidates. Additionally, when there was little evidence to identify whether a preclinical candidate is at the advanced preclinical stage, we again erred on the side of being inclusive so we could get an 'upper bound' estimate of costs and a conservative estimate of launches.

2.2 Classifying candidate therapeutics into archetypes and levels of complexity

Once these therapeutic candidates were identified, the next step was to classify each candidate by its archetype and level of complexity (Table 2). Guidance on how to classify candidates is included in the P2I model[15]. In terms of "archetype", therapeutics are categorized as repurposed drugs, NCEs, or biologics. These archetypes were further sub-divided by level of complexity as simple and complex, mostly based on whether the development approach is novel or has already been validated (Table 2). For each of the six archetypes in Table 2 (simple repurposed drug, complex repurposed drug, simple NCE, complex NCE, simple biologic, complex biologic), the P2I model has distinct assumptions on the costs, attrition rates, and cycle times per phase (Table 3). If the

candidate included components of more than one archetype (e.g., one candidate was a combination of lopinavir/ritonavir and interferon beta-1b, which was initially classified as a repurposed drug plus a biologic), it was classified according to its most complex component. For descriptive purposes, we noted whether biologics were synthetic or biological (the P2I model treats these as the same when it comes to cost, attrition rate, and cycle time per phase). The classification process was completed by PCR on January 21st, 2019.

Table 2: Description of Therapeutic Archetypes and Levels of Complexity

Drug Archetype		Description	Examples
Repurposed drug	Simple	Drug has sufficient safety data to start development in phase II	azithromycin, doxycycline
	Complex	Drug requires some phase I clinical trials to verify safety in humans	moxidectin
NCE	Simple	Validated target/mechanism of action	primaquine
	Complex	Novel target/mechanism of action without understanding of disease pathogenesis	imatinib
Biologic	Simple	Development from a combination of two broadly neutralizing antibodies that have been developed independently first	human monoclonal antibody m102.4
	Complex	Developing a new broadly neutralizing antibody	polyclonal IgG antibodies

Source: http://www.who.int/tdr/publications/r_d_report/en/

Table 3: Assumptions on Costs, Attrition Rates, and Cycle Times per Phase

Drug Archetype		Costs per phase ($, Millions)				Attrition rates per phase (%)				Cycle times per phase (years)			
		Preclinical	Phase I	Phase II	Phase III	Preclinical	Phase I	Phase II	Phase III	Preclinical	Phase I	Phase II	Phase III
	Simple	5.0	2.2	5.8	17.6	75.0	59.0	46.0	68.0	2.3	1.6	2.1	2.1

Repurposed Drug	Com-plex	5.0	2.2	5.8	17.6	75.0	59.0	46.0	68.0	2.3	1.6	2.1	2.1
NCE	Simple	5.0	2.2	5.8	32.8	65.0	60.0	39.0	69.0	2.5	1.8	3.4	3.2
	Com-plex	10.0	7.4	6.4	36.1	55.0	57.0	20.0	40.0	2.9	1.9	3.5	2.8
Biologic	Simple	6.7	2.2	13.2	122.0	41.0	68.0	46.0	70.0	3.4	1.6	2.2	3.1
	Com plex	16.6	2.5	13.9	126.0	41.0	50.0	22.0	40.0	3.3	2.0	3.7	2.8

Source: https://gatesopenresearch.org/articles/2-23/v2

2.3 Inputting the pipeline into P2I model

After classifying all therapeutic candidates into their archetype, complexity level, and development phase we input them "prospectively" into the Microsoft Excel-based P2I model. The model assumes that each candidate is at the start of its development phase (e.g., if a candidate is in phase II, the model assumes it is at the start of phase II). The Excel tool has built-in assumptions on costs, attrition rates and cycle times per phase for each different archetypes, and the financial formulae are also built in (Figure 1). We input the candidates into the Excel, and ran the model, which yielded three outputs: a) *Output 1:* estimates of expected costs of moving candidates through the pipeline from their current phases, b) *Output 2:* the estimated number of anticipated launches, and c) *Output 3:* which critical, highly needed products will still be "missing" at the end of this process.

The development of the P2I model is described in a paper by Robert Terry and colleagues at TDR and CPIGH[13]. The model (or financial modeling tool) is based on

assumptions about development costs, attrition rates, and cycle time per phase for each different type of archetype. As noted by Terry et al., "the assumptions on development costs at each phase were initially based on a bottom-up analysis of clinical trial costs from Parexel's R&D cost sourcebook," and these were then refined and validated based on 133 stakeholder interviews. Terry et al. state that "assumptions on attrition rates and cycle times at each phase were initially based on a review of over 25,000 development candidates for attrition rates and cycle time."

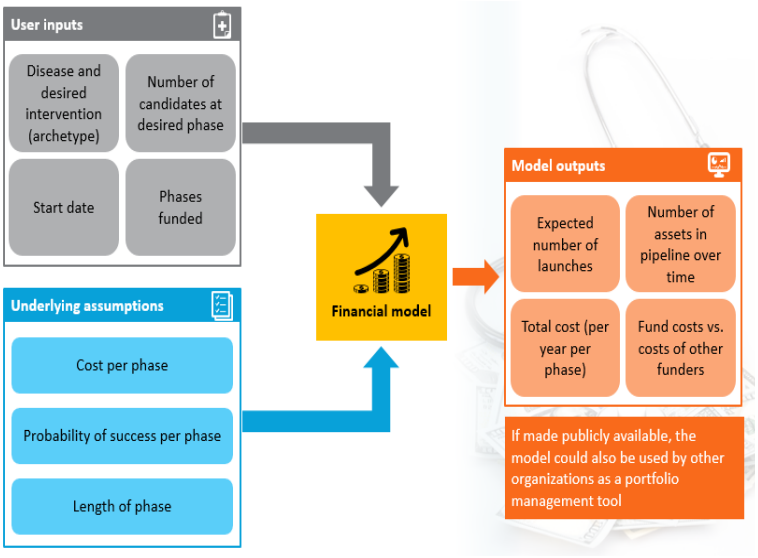

Figure 1: Conceptual Overview of P2I Finance Model[11]

The cost estimates included in the P2I model include direct expenses, workforce costs, clinical supplies, internal headcount costs and nonmonetary in-kind contributions. These estimates exclude the cost from basic research to lead optimization; Good Manufacturing Practice (GMP) manufacturing infrastructure- and scale-up costs; the

cost of manufacturing; regulatory or registration fees; any post-marketing costs; and any capacity building costs associated with the product.

The original version of the P2I model (or P2I v.1 model) was based on assumptions about the cost, probability of success, and cycle time per phase for eleven different archetypes[13]. Several types of adaptions were made in version 2 (or P2I v.2 model), which was used for a study of the pipeline of candidates for 35 neglected diseases[15]. The adaptations included a) adding additional archetypes (i.e., other vector control products and an archetype called 'unprecedented vaccines,' referring to vaccines for HIV, tuberculosis, and malaria), b) adapting some of the assumptions related to TB product development, and c) modifying a small number of the original assumptions based on data from the Bill & Melinda Gates Foundation[15]. Details of these adaptions have been described elsewhere[15]. Since our study only focuses on therapeutic candidates for the 10 Blueprint pathogens, we used the initial description of each archetype from the P2I v.1 model for the classification process, and we used the P2I v.2 model with updated assumptions for the financial modeling exercise. In addition, we made our own adaptation to the custom-built P2I v.2 model (i.e., adding Blueprint pathogens to the disease list), in consultation with technical experts, so that it was better suited to the pipeline for emerging infectious diseases with pandemic potential.

The P2I model assumes that all candidates are at the beginning of their development stage. We ran the model with a start date of 2019 (i.e., beginning with the

current pipeline, and then projecting forward in time from the present). We did not use discounting for our cost estimates.

For *output 1* (i.e., the costs to advance the current portfolio of candidates through the pipeline from 2019 onwards), we presented the results in four ways:

i) total costs to advance the current portfolio through the pipeline

ii) total portfolio costs by development phase

iii) total portfolio costs by archetype

iv) total portfolio costs by disease target.

For *Output 2 (i.e.,* the anticipated product launches that would result from advancing the pipeline of candidates), we presented the results in two ways:

i) estimated number of launches across all disease targets/archetypes

ii) estimated number of launches without rounding by disease target and archetype.

For *output 3 (i.e.,* which critical, highly needed products will still be "missing" at the end of this process*)*, we present the additional costs to ensure that at least one therapeutic is launched for each of the ten Blueprint diseases (the method for estimating these costs is described in Section 2.4 below).

2.4 Estimating the costs of developing "missing" products

First, for those disease archetypes with no candidates in the current pipeline, we estimated the number of candidates that would be needed at the preclinical stage to lead

to one product launch, based on the assumptions of attrition rates. For example, based on the P2I model assumptions on attrition rates (Table 3), if there were zero simple biologic candidates in the current pipeline for disease X, a total of 12 candidates would be needed at the preclinical stage to lead to one product launch. Then we inputted the estimated number of preclinical candidates (i.e., 12) "retrospectively" into the P2I v.2 model; the model then estimates the costs to advance these simple biologic candidates through the pipeline to lead to one likely launch.

Second, in cases where there were candidates in the pipeline for a specific disease, but the final number of launches was under 1, we estimated the additional number of preclinical candidates that would be needed to lead to at least one launch. For example, if there were already several simple NCE candidates for disease X in the pipeline, and the model suggested that these candidates would lead to 0.7 launches, we estimated the number of additional candidates needed at the preclinical phase and the associated additional costs to develop an additional 0.3 launches.

Overall, for *output 3*, we used these two approaches to estimate the additional costs to launch at least one therapeutic for all ten Blueprint diseases.

2.5 Sensitivity analysis

Finally, we conducted a sensitivity analysis using an approach developed by the United Kingdom Office of Health Economics.[18] In the sensitivity analysis, we examined the impact on costs and launches of: 1) changing all probabilities of success per phase to

10% higher and 10% lower; 2) changing all costs per phase to 10% higher and lower; 3) changing all possible combinations of 1) and 2).

3. Results

3.1 Pipeline portfolio review of candidate therapeutics for the 10 Blueprint priority diseases

From an initial retrieval of 13488 records identified through database searching, a total of 13410 records were excluded based on the following criteria: a) *Disease category*: vaccines (e.g., therapeutic vaccines), diagnostics, or other products (e.g., insecticides or bed nets); b) *Development phase:* projects were at an early discovery stage (or at the stage of concept and research), or therapeutic products had already been granted regulatory approval; c) *Duplicates:* duplicates with different renderings of identical candidate names (e.g., IMM 010, IMM-010 and IMM010), or duplicates listed under different names (e.g., ranpirnase, onconase and P-30 protein*); d) Missing values:* potential candidates were designated in the Citeline Pharmaprojects database or clinical trial registries as "not applicable," "discontinued" or "on hold," candidates with missing values, or with no development report, or lack of information for making a decision about how to categorize them into archetypes, e) *Drug class (i.e., a set of medications that are grouped because of their similar therapeutic use, mechanism of action, mode of action, and/or chemical structure*[20]*):* conflicting evidence on candidate class, f) *Efficacy:* research generated inconclusive or no evidence, g) *Route of administration:* listed route of administration incorrect or not recommended.

Figure 2 shows the process by which we finally identified 78 therapeutic candidates as of December 3rd, 2018 for inclusion in the P2I model (i.e., steps 2-5).

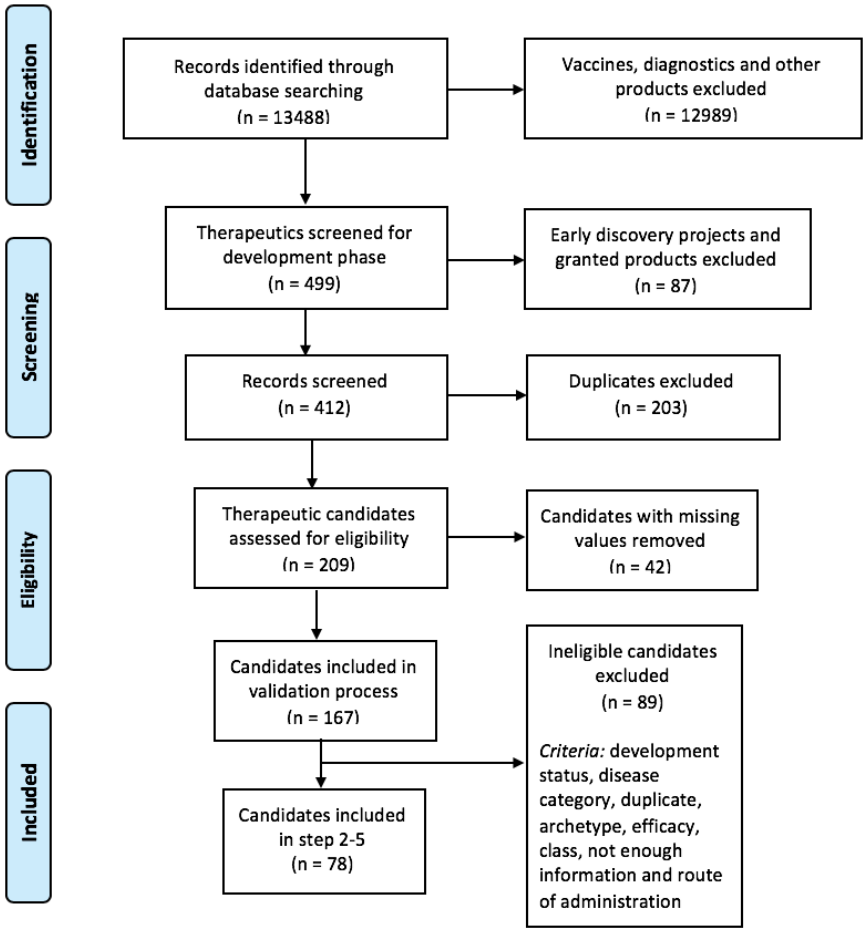

Figure 2: PRISMA Flow Diagram of Pipeline Portfolio Review[21]

Out of a total of 78 candidate therapeutics, Zika (41.0%) and Ebola (30.8%) dominated the current pipeline, as shown in Figure 3. In contrast, the other Blueprint pathogens have very few candidates under development, despite having high outbreak potential. For CCHF, SARS, and Nipah virus, we identified no candidates at all under development as of December 3rd, 2018.

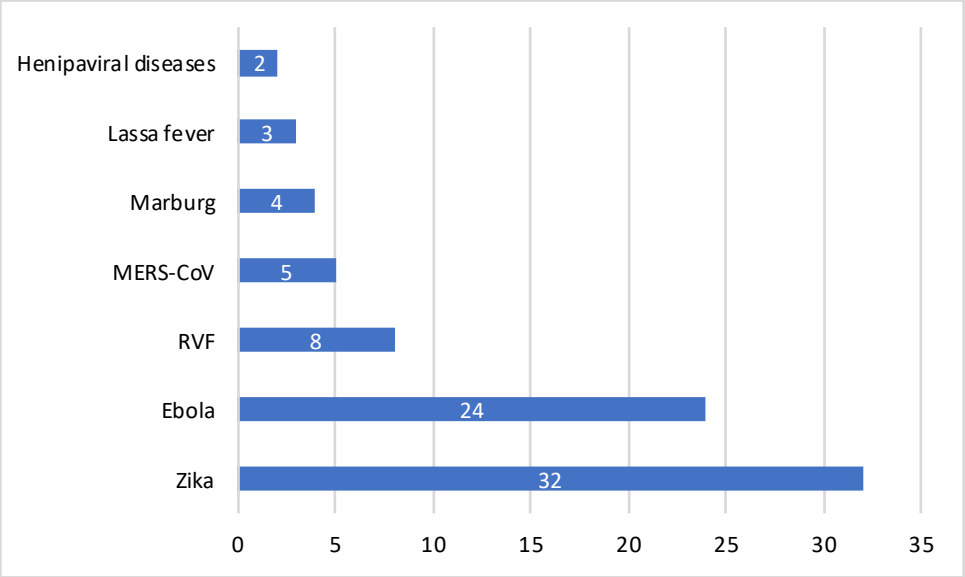

Figure 3: Number of Candidate Therapeutics by Priority Pathogens

Figure 4 presents a breakdown of candidate therapeutics by archetype and complexity. Based on our pipeline portfolio review, we identified 40 biologics, 25 repurposed drugs and 13 NCEs. Candidates classified as simple (53.8%) and complex (46.2%) were fairly even distributed.

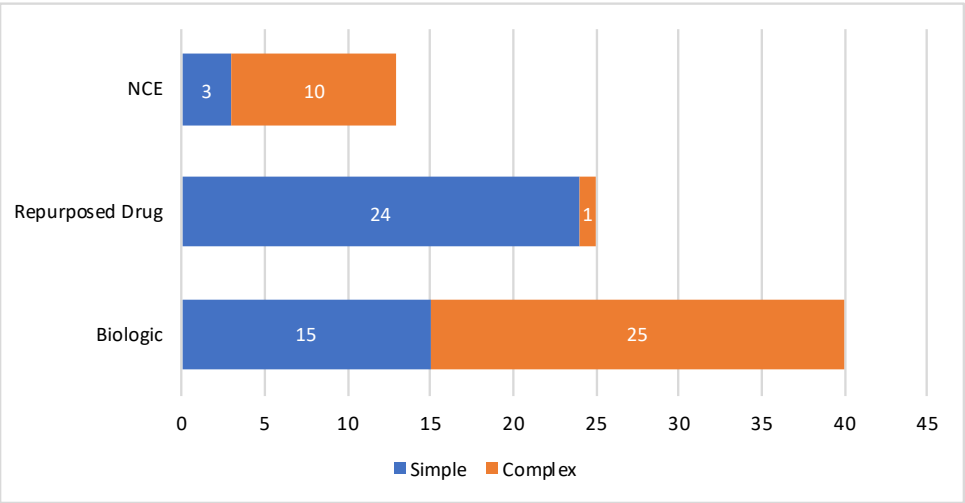

Figure 4: Number of Candidate Therapeutics by Archetype and Complexity Level

Figure 5 summarizes the distribution of candidate therapeutics for the priority pathogens by archetype and complexity level. None of the Blueprint diseases have all six archetypes under development (simple and complex repurposed drugs, simple and complex NCEs, and simple and complex biologics). Six out of the seven diseases shown in Figure 5 had simple biologic candidates under development. The most common products under development are simple repurposed drugs for Zika (n=12 candidates) and complex biologics for Ebola (n=10 candidates).

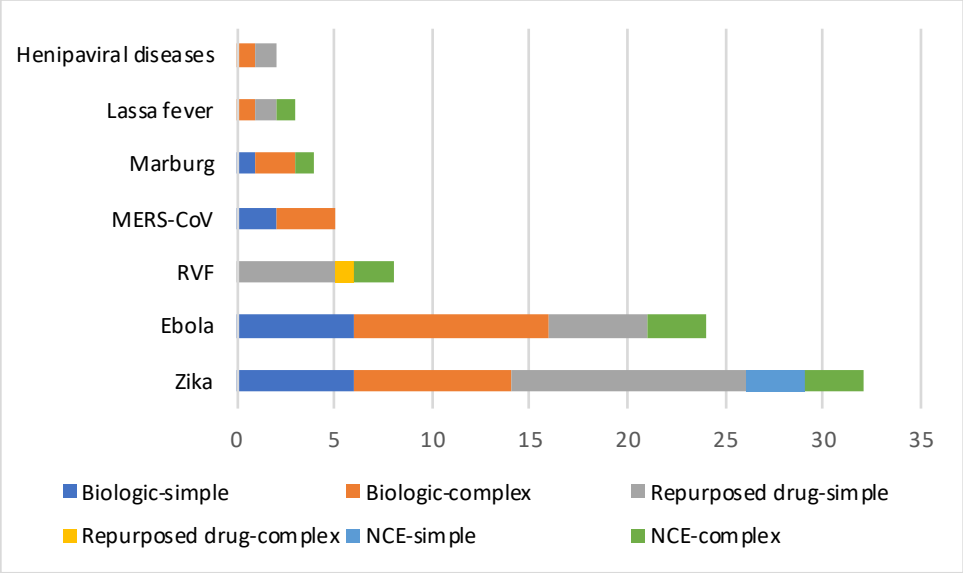

Figure 5: Number of Candidate Therapeutics for Priority Pathogens by Archetype and Complexity Level

The distribution of candidates by the four development phases is shown in Figure 6. Most candidates in the pipeline are currently at the preclinical phase. Just over half (53%) of all preclinical candidates were for Zika. Ebola and RVF are the only two Blueprint diseases that have candidates (one candidate each) in phase III.

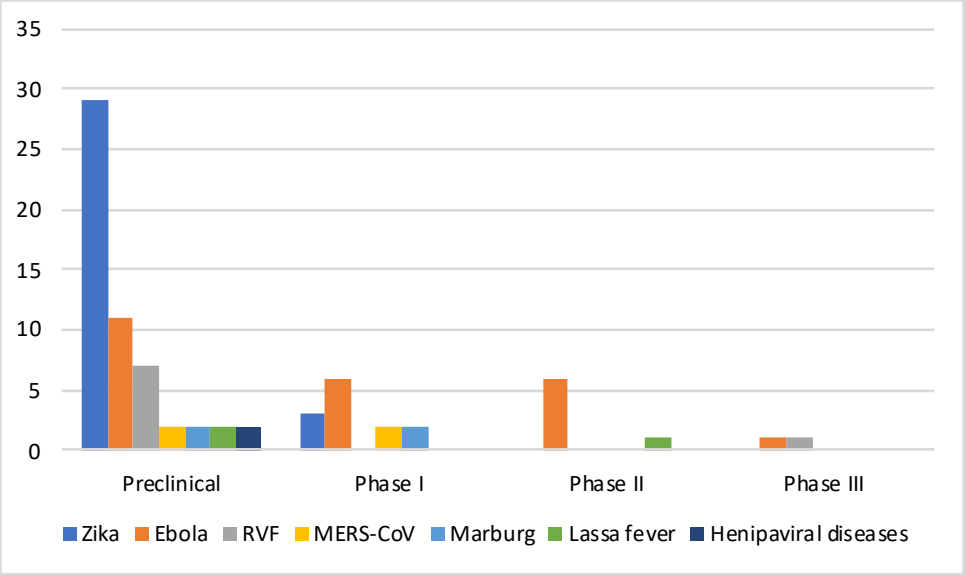

Figure 6: Number of Candidate Therapeutics for Priority Pathogens by Development Phase

3.2 Expected costs of moving candidates through the pipeline from their current phases

After inputting the 78 candidates into the P2I model, the model estimated that it would cost $1.76 billion to move these candidates through the pipeline from 2019 to 2030. Figure 7 shows the breakdown of these costs over time and by archetype. About 61% of the costs would be incurred in the next 5 years (i.e., the costs would be front loaded). Of the total costs to move the current portfolio through the pipeline, 69% of the costs would be for biologics ($1.22 billion), 19% for repurposed drugs ($0.33 billion), and 12% for NCEs ($0.21 billion). The total portfolio costs would be roughly evenly distributed across simple (53.8%) and complex (46.2%) candidates, in line with the even distribution of simple and complex candidates. The costs are dominated by Ebola (37%, or $0.7B of the total costs) and Zika (36%, or $0.6B of the total costs). These costs would

be about 18 times the cost of moving the current candidates for henipaviral diseases through the pipeline (2%, or $0.04B of the total costs). Looking at the total costs by development phase, over half of the costs would be for phase III clinical trials ($0.8B). The remaining costs would be $0.5B for advanced preclinical, $0.3B for phase II, and $0.1B for phase II.

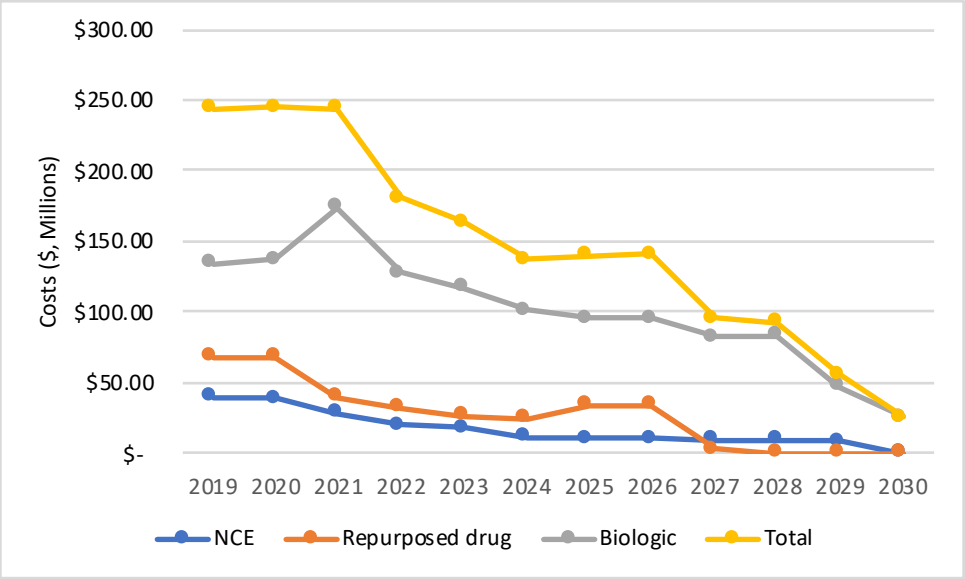

Figure 7: Trends in Development Costs Over Time, Total and by Archetype

3.3 Anticipated product launches that would result from advancing current candidates through the pipeline

Our modeling suggests that across all 10 diseases and all archetypes, there would be a total of 8.78 product launches, dominated by simple biologics (n=2.30) and simple repurposed drugs (n=4.92). For all other archetypes, there would be less than one anticipated launch. Figure 8 below shows the estimated number of launches by disease and archetype. The three diseases that are likely to have the most product launches are

Ebola (3.21), Zika (2.91), and RVF (1.42); this pattern aligns with the fact that the current pipeline of candidates is dominated by these three diseases. For all the other diseases, there would be less than one anticipated launch.

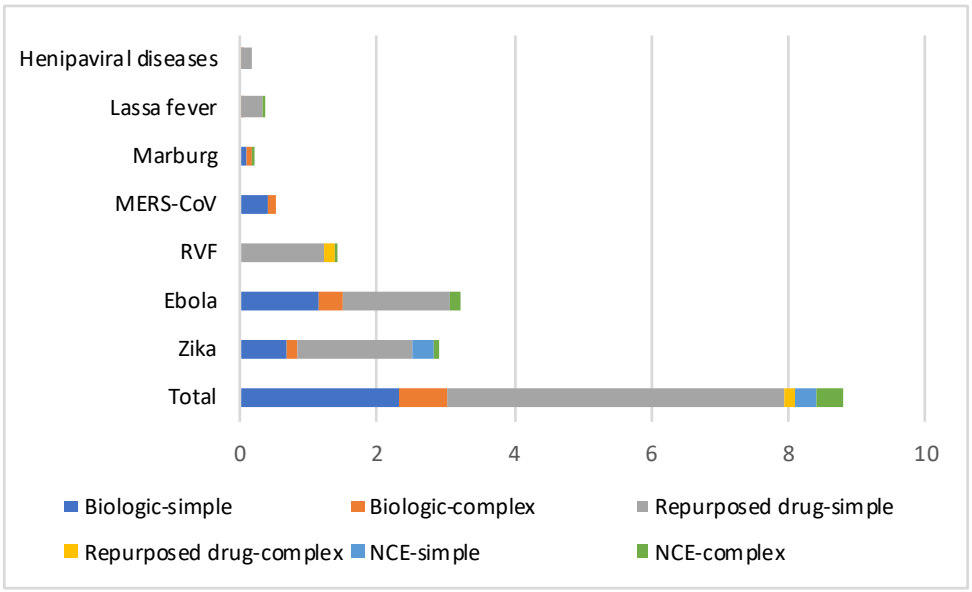

Figure 8: Cumulative Number of Launches for Priority Pathogens, Total and by Archetype

Table 4 is a waffle table that shows which critical, highly needed products would still be "missing" given the current pipeline of candidates and the results of the P2I modeling. *Green* indicates that there is likely to be at least one product launch for that archetype and disease (i.e., at least one simple biologic for Ebola and at least one simple repurposed drug for Ebola, Zika, and RVF). *Orange* indicates that there would less than one but more than zero launches for that archetype and disease (e.g., for MERS-CoV, there would be less than one but more than zero launches of both simple and complex biologics). *Blue* indicates where there were zero candidates in the pipeline and thus zero launches. Given that we are likely to see launches of at least one therapeutic for Ebola,

Zika, and RVF, for the purposes of this study we considered that the "missing products" were a therapeutic for each of the remaining seven Blueprint diseases (i.e., the blue and orange products for these other seven diseases).

Table 4: Waffle Table of "Missing" Products by Disease and Archetype

⩾ 1 product launches	0 < product launches < 1	0 product launch

Disease	Biologic-simple	Biologic-complex	Repurposed-simple	Repurposed-complex	NCE-simple	NCE-Complex
Zika						
Ebola						
RVF						
MERS-CoV						
Marburg						
Lassa fever						
Henipaviral						
CCHF						
SARS						
Nipah virus						

3.4 Estimates of the costs of "missing" products

For each disease archetype with a "missing" product, we estimated the number of additional preclinical candidates that would be needed to lead to one anticipated launch of this archetype and the associated costs (Table 5, $ Millions). Our study found that while the current pipeline is likely to lead to launches of therapeutics for three of the Blueprint diseases—Ebola, Zika, and RVF—it is unlikely that there would be launches for the other seven diseases. For these 7 diseases with either no candidates in the pipeline (in blue), or there are too few candidates to reach a likelihood of one launch (in orange), the additional cost to launch at least one therapeutic ranges from $63.94

million to $1463.60 million dollars, depending on the complexity of the candidate. The cost range for developing one of the disease archetypes is summarized in Figure 9.

Table 5: Number of Additional Preclinical Candidates and Associated Costs

Disease	Biologic-simple		Biologic-complex		Repurposed-simple		Repurposed-complex		NCE-simple		NCE-Complex	
	No.	Cost	No.	Cost	No.	Cost	No.	Cost	No.	Cost	No.	Cost
MERS-CoV	7	188.33	50	1306.78	8	102.31	8	102.31	10	136.69	40	733.07
Marburg	11	295.95	52	1359.05	8	102.31	8	102.31	10	136.69	40	733.07
Lassa fever	12	322.86	55	1437.46	5	63.94	8	102.31	10	136.69	39	714.74
Henipaviral	12	322.86	36	940.88	7	89.52	8	102.31	10	136.69	40	733.07
CCHF	12	322.86	56	1463.60	8	102.31	8	102.31	10	136.69	40	733.07
SARS	12	322.86	56	1463.60	8	102.31	8	102.31	10	136.69	40	733.07
Nipah virus	12	322.86	56	1463.60	8	102.31	8	102.31	10	136.69	40	733.07

For those archetypes with less than one but more than zero anticipated product launches (shown in orange in Table 4), the most costly product development would be a complex biologic for Lassa fever, which would require an estimated additional 55 candidates at the preclinical phase and an additional $1437.46 million to fund one launch. The least costly product development would be to develop a simple repurposed drug for Lassa fever, would require an additional 5 candidates at the preclinical phase and an additional $63.94 million to fund one launch. The lower bound of the cost range is for simple archetypes targeting any disease, while the upper bound of the cost range is for complex archetypes for every pathogen.

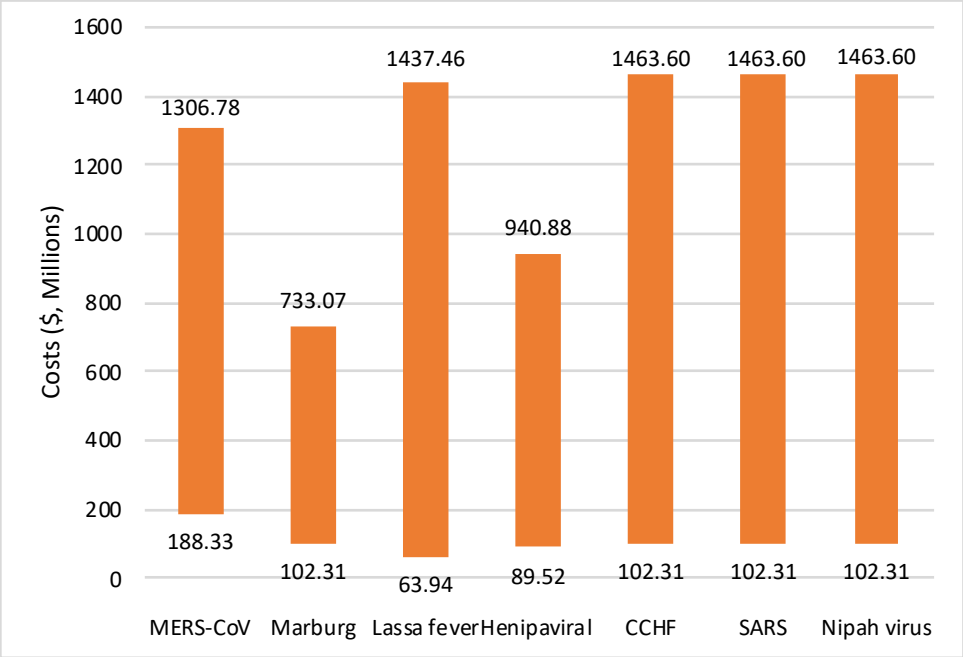

Figure 9: Cost Range for Developing "Missing" Products by Disease

For those disease archetypes with no candidates in the current pipeline (shown in blue in Table 4), the number of candidates needed at the preclinical stage to lead to one product launch and the associated costs by archetype and complexity level are shown in Table 6 (associated costs by 3 diseases are also seen in Figure 9). In the P2I model, the assumptions on costs, probability of success, and time per phase are developed based on archetype and complexity, and not on pathogen (i.e., the assumptions shown in Table 6 apply to development of therapeutics for *any* of the 10 Blueprint pathogens). The most costly product development would be to develop a complex biologic, which requires an additional 56 candidates at the preclinical phase and an additional $1463.60 million to fund one launch. The least costly product development would be to develop either a simple or complex repurposed drug, which

requires an additional 8 candidates at the preclinical phase and an additional $102.31 million to fund one launch. Figures for simple and complex repurposed drug are the same in table, because they have identical assumptions in the P2I model.

Table 6: Estimates of the Number of Product Candidates Needed at Preclinical Phase and the Development Cost to Launch One Product, by Archetype, Assuming Pipeline is Empty

Drug Archetype		Number of candidates needed at preclinical phase	Costs to launch one product ($, Millions)
Repurposed drug	Simple	8	102.31
	Complex	8	102.31
NCE	Simple	10	136.69
	Complex	40	733.07
Biologic	Simple	12	322.86
	Complex	56	1463.60

3.5 Sensitivity analysis

Table 7 below shows the results of sensitivity analysis. In this analysis, we tested the effect of changing all probabilities of success per phase to 10% higher and 10% lower, all costs per phase to 10% higher and lower, and all possible combinations of these changes. Our sensitivity analysis found that the total costs to advance the current candidates through the pipeline range from $1.4-2.2 billion and the anticipated number of launches ranges from 6.48-11.71.

Table 7: Sensitivity Analysis

Drug Archetype		Cumulative launches	Costs ($, Millions)
Probability of success	Low (-10%)	6.48	1563.40
	High (+10%)	11.71	1992.98
Cost per phase	Low (-10%)	8.78	1587.83
	High (+10%)	8.78	1940.68
Combinations of changing probability of	Probability of success (-10%); Cost (-10%)	6.48	1407.06

success and cost per phase	Probability of success (-10%); Cost (+10%)	6.48	1719.74
	Probability of success (+10%); Cost (-10%)	11.71	1793.69
	Probability of success (+10%); Cost (+10%)	11.71	2192.28

4. Discussion

Our pipeline portfolio review identified 78 candidate therapeutics for the 10 Blueprint diseases as of December 3rd, 2018. Financial modeling of this portfolio using the P2I model suggests that it would cost an estimated $1.76 billion to move these 78 candidates through the pipeline. The model estimates that this level of investment would lead to 8.78 product launches, dominated by simple biologics and simple repurposed drugs. About 61% of the total costs would be incurred in the next 5 years.

The pipeline of therapeutic candidates is dominated by Zika (38% of all candidates) and Ebola (29% of all candidates). It is likely that this dominance reflects urgent and rapid mobilization of funding for product development in response to the recent high-profile epidemics of these diseases. For example, in its annual survey of funding for product development for neglected diseases (the G-FINDER survey), Policy Cures Research found a sharp rise in annual funding for Ebola product development from 2013 to 2015 in the wake of the 2014 west African epidemic (Figure 10[22]). In contrast, the seven other Blueprint pathogens have very few or no candidates under development, despite having high outbreak potential. This lack of candidates in the pipeline for so many of the Blueprint diseases means that there is unlikely to be product launches for these diseases in the near term, leaving the world vulnerable to uncontrollable epidemics.

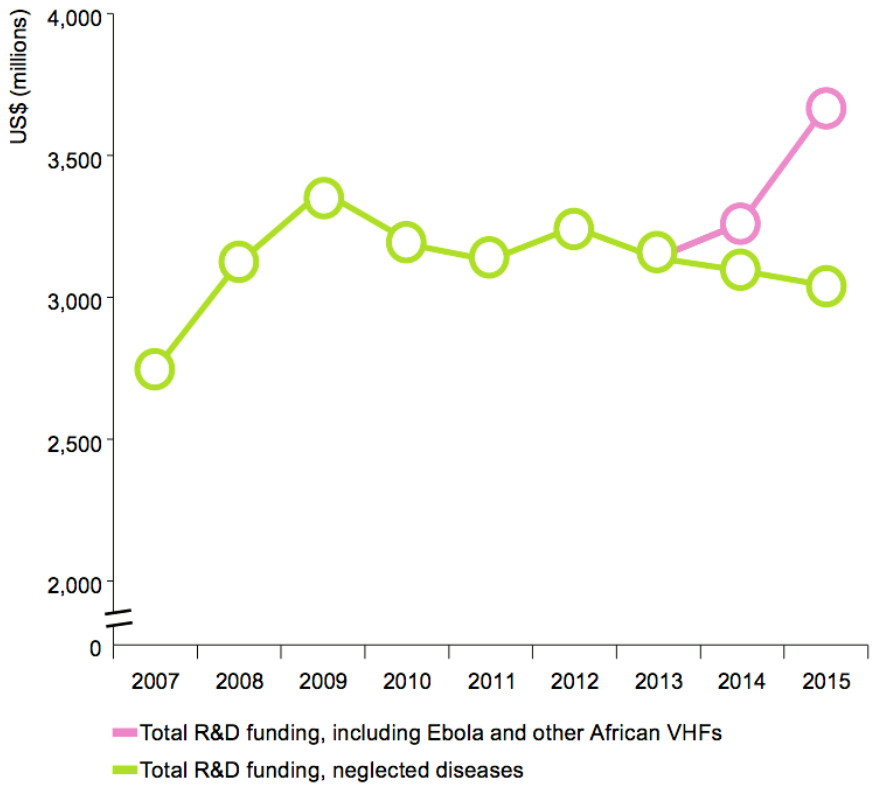

Figure 10: Total R&D funding with Ebola and other Africa Viral Haemorrhagic Fevers (VHFs) 2007-2015[22]

It is unclear how our estimate of the costs of advancing the current pipeline of candidates ($1.76 billion) compares with how much is actually being spent—thus we do not know if there is a funding gap. As mentioned, the model estimates that 61% of these costs, i.e., $1.07 billion, would be incurred in the first 5 years, which is an annualized average of $215 million. It is unclear whether annual spending on development of therapeutics for the ten Blueprint diseases matches this need, since there have been no studies conducted on quantifying such annual spending. In 2019, Policy Cures Research will begin the first ever study to quantify annual total spending on development of all product types (therapeutics, vaccines, diagnostics) for the ten Blueprint diseases (Nick

Chapman, Policy Cures Research, personal communication). The results of the new Policy Cures Research study will allow researchers and funders to assess the size of the product development funding gap for the Blueprint diseases. Nevertheless, it does seem likely that there is under-investment in developing therapeutics for several of the Blueprint diseases—most funding is likely to be directed at Ebola and Zika.

Our study estimated the additional costs to launch "missing" therapeutics. With the exception of Ebola, Zika, and RVF, for all other Blueprint diseases, there were either no candidates in the pipeline (thus launches are impossible) or there were too few candidates in the pipeline to reach a likelihood of at least one launch (i.e., the model suggested there would be over 0 but under 1 launch). We estimate that it would require an additional $0.64 billion to $1.46 billion to launch at least one therapeutic for those seven diseases, depending on the complexity of the product. Thus the total funding needs to ensure a therapeutic for all ten Blueprint diseases are substantial. It is likely that a major effort will be needed to mobilize this level of funding. While CEPI has mobilized over $740 million to develop vaccines to control the Blueprint diseases[23], there is no similar mechanism to mobilize funding for development of therapeutics.

4.1 Study strengths

To the best of our knowledge, our study is the first to (a) examine which therapeutic candidates are currently in the pipeline for 10 Blueprint diseases; and (b) estimate development costs from advanced preclinical to phase III and the likely

product launches, based on the portfolio as of December 2018. The model outputs help to determine which critical, highly needed candidates will still be missing based on the current pipeline of candidates. These results could help to mobilize additional funding and target it to where pipeline is most lacking.

Moreover, our study also estimates the number of additional preclinical candidates and associated costs that are needed to develop at least one product launch for all Blueprint diseases. This information can be helpful in advocating for additional funding to develop medical countermeasures against epidemics.

4.2 Study limitations

Our study has at least five limitations:

1) *The pipeline changes quickly and we only captured a snapshot in time.* Our pipeline portfolio review identified 78 candidates as of December 3rd, 2018. But the product development pipeline changes quickly, and so today's pipeline may already differ from what we found.

2) *Our pipeline portfolio review is likely to have underestimated the total number of candidates*. Our pipeline portfolio review is unlikely to be 100% complete, especially for preclinical candidates. It is widely acknowledged that drug companies do not disclose products under development until studies reach clinical trials, when they must then be registered in publicly accessible clinical trial registries. There is no requirement for companies to publicly disclose candidate products undergoing pre-clinical

development. Although we did our best to search a wide variety of databases and trial registries, we probably missed some candidates under development. Thus, overall our model results probably under-estimates the total costs and likely launches. .

3) *The P2I model does not have a category for combination therapies.* Since there is no archetype or category in the model for combination treatments, users must categorize any combination therapy into an existing archetype (i.e., a combination must be categorized into a simple or complex repurposed drug, a simple or complex NCE, or a simple or complex biologic). Yet the costs, attrition rates, and cycle times for combination therapies probably differ from those of non-combination (single) treatments. We addressed this limitation by erring on the side of being conservative, and choosing to categorize combination therapies by the most complex component. For example, for candidate ID 75, which is a combination of lopinavir/ritonavir (repurposed drugs) and interferon beta-1b (a simple biologic), in the P2I model, we classified it as a simple biologic, which has a higher attrition rate and higher cost of development than repurposed drugs. In this way, we were able to derive an 'upper bound' estimate of costs and a conservative estimate of launches.

4) *The P2I model treats synthetic and biological biologics as the same*. When it comes to the underlying assumptions about costs, attrition rates, and cycle times per phase, the model uses the same assumptions for synthetic versus biological biologics. Yet in reality these assumptions may differ.

5) *The P2I model does not include all phases of research and all research costs:* The P2I model includes candidates from the advanced preclinical phase to phase III. It excludes other costs, such as at the costs of basic research and drug discovery, which can be substantial[24].

5. Conclusion

Previously published estimates of the price tag to develop MCMs assume that the pipeline is empty. The P2I model allows user to input a portfolio of candidates currently under development and to make adaptations to the model's archetypes and underlying assumptions. Our study found that while the current pipeline is likely to lead to launches of therapeutics for three of the Blueprint diseases—Ebola, Zika, and RVF—it is unlikely that there would be launches for the other diseases.

We hope these results will help to mobilize additional financing and to inform new funding mechanisms, which are urgently needed for emergency response and preparedness against the highest threat diseases. We also hope that the study results will help identify where the pipeline has gaps, so that funding can be better directed to areas of greatest need.

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