PREPARED UNDER
ERG TASK ORDER NO. HHSP23337004T
ERG CONTRACT NO. HHSP233201500055I
AND
UNDER SUBCONTRACTS TO
MATHEMATICA POLICY RESEARCH & NORC

PREVENTIVE VACCINE DEVELOPMENT

FINAL

SUBMITTED TO:
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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NOVEMBER 29, 2022

ACKNOWLEDGMENTS

We gratefully acknowledge Amber Jessup (HHS/OIG/OMP) and Trinidad Beleche (HHS/OS/ASPE) for their leadership, guidance, and input throughout this study. We also would like to thank all of our expert panel members for their input on the potential impacts of different strategies on medical product development costs. Many others involved in clinical research, including pharmaceutical/biopharmaceutical company representatives, CRO personnel, and industry experts, provided valuable information for the study. We are grateful to them all for sharing their opinions and experiences with us. We also would like to acknowledge Hui-Hsing Wong (ASPR/BARDA), Chazeman Jackson (formerly at HHS/ASPE), Jessica White (HHS/ASPE), and the anonymous NIH and FDA experts for their review and feedback on different aspects of the study.

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LIST OF ACRONYMS

BLA	Biologics License Applications
CROs	Contract research organization
DHHS	Department of Health and Human Services
eNPV	Expected net present value
EHR	Electronic health record
ERG	Eastern Research Group, Inc.
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
IRB	Institutional review board
NIH	National Institutes of Health
NPV	Net present value
OCOC	Opportunity Cost of Capital
POS	Probability of success
PVac	Preventive vaccine
SDV	Source data verification
WHO	World Health Organization

EXECUTIVE SUMMARY

The cost of bringing a medical product to the U.S. market has been increasing and clinical trials constitute a large portion of these costs. In preventive vaccine development, the clinical phase lasts an average of around 111 months compared to 64 months for the non-clinical phase and accounts for between 90 to 95 percent of overall R&D costs (Wilson, 2010; World Health Organization, 2016). Clinical trials contribute significantly to the rising cost trend as they have become more expensive, complex, and lengthier over time. Thus, there is ongoing interest in reducing the overall cost of medical product development by improving the efficiency of clinical trials conducted in support of regulatory submission for marketing approval.

This study quantified the potential impacts of the following strategies on the cost, duration, and phase transition probability associated with preventive vaccine development stages:

- **Mobile technologies—**Mobile technologies can include cell phones, wearable trackers, and other devices that capture data directly from patients. Electronic data capture means capturing study data in electronic format. The strategy could entail encouraging the use of mobile and other technologies in clinical trials and the development process as a whole and clarifying requirements around their use.

- **Simplified clinical trial protocols and reduced amendments—**The strategy could entail encouraging sponsors to simplify clinical trial protocols, where possible, ensuring that they have a clear understanding of what is required by FDA and what is superfluous.

- **Reduced source data verification (SDV)—**Source data verification is the process of comparing data collected throughout the clinical trial to the original source of information to verify data integrity. The strategy could entail engaging sponsors in discussions on the topic of data and site monitoring to ensure that they are aware of the FDA guidance stating that 100 percent source data verification is not required, as well as continuing to educate reviewers on this policy.

- **Improvements in FDA review efficiency and interactions—**The strategy could entail providing more opportunity to identify, discuss, and resolve substantive issues during the review, continuing to educate FDA reviewers on changes in FDA policy, and providing more transparency about what endpoints are required. However, the strategy does not account for the additional resource burden on FDA associated with implementing these strategies.

- **Staged approval—**Staged approval could entail granting provisional marketing approval to market a preventive vaccine after safety and basic efficacy have been shown, and then continuing to collect additional safety and efficacy data. This would allow the product to be marketed in the United States for use in limited

patient populations, and then gradually expand use to additional patient populations as more data to support safety and efficacy in those populations are collected.

- **Biomarkers as surrogate endpoints—**Biomarkers as surrogate endpoints are biological indicators that may correlate with the desired clinical endpoint, for example when it would take a long time for the clinical endpoint to become evident. The strategy could entail clarifying the path to biomarker validation or encouraging collaboration between academics, public entities, and industry to develop and validate biomarkers for use as surrogate endpoints.

- **Electronic health records—**EHRs, used here as being synonymous with electronic medical records (EMRs), are digital versions of the data collected when a patient visits a healthcare provider's office. The strategy could entail encouraging sponsors to use EHRs for patient and physician recruitment or to collect clinical endpoints.

- **Patient registries—**A patient registry is an organized system that uses observational study methods to collect uniform data to evaluate specified outcomes of a disease or condition for a population. Registries include those established by a patient organization for a particular disease as well as registries that are sometimes established by the manufacturer and used as a post-marketing study. The strategy could entail encouraging sponsors to use registry data for patient and physician recruitment or to collect clinical endpoints for use in a clinical trial, where possible.

- **Adaptive design—**An adaptive design allows modifications to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity. The strategy could entail clarifying FDA's policies on whether certain types of adaptive trial design are acceptable and encouraging their use.

- **Standardized contracts—**Standardized contracts are contract templates for use in sponsor-initiated multi-site trials, intended to reduce the complexity and duration of contract negotiations for clinical trial studies. The strategy could entail encouraging the use of master contracts and standardized contracts or compiling existing resources into a central location.

- **CDC/NIH developing epidemiological data on disease incidence—**This strategy would entail CDC and/or NIH collecting epidemiological data on disease incidence that is tailored to developing vaccines, rather than each vaccine manufacturer collecting it individually.

- **Federally supported cGMP-compliant manufacturing facilities—**Vaccines must be produced in cGMP-compliant facilities before they can be administered to human patients in clinical trials. However, the number of cGMP-compliant bioproduction facilities operating in the U.S. is limited which can be disruptive to clinical development programs making them more expensive. This strategy would entail

providing additional funding or other support to help increase the number/capacity of cGMP-compliant manufacturing facilities that can produce batches of vaccines for use in clinical trial studies.

The strategies listed above were identified via a literature review conducted during the 2016-2018 period and many overlapped with those identified in the 2014 study. Since that time, several of the strategies included herein were adopted and additional strategies have emerged, such as remote patient monitoring and virtual visits, which gained widespread adoption due to the COVID-19 pandemic. Additionally, recognizing the challenges of conducting clinical trials during a public health emergency, FDA issued new guidance containing nonbinding recommendations on a range of issues, including the use of virtual patient visits, remote monitoring of clinical sites, and use of real-world data in medical product applications (U.S. Food and Drug Administration, 2021a). Given the timing of the literature review and analyses, this report does not address these new developments.

To facilitate the evaluation of the above-mentioned strategies, the study also included the development of a cost model for drugs. The model used data from a variety of sources (public and non-public) and widely accepted accounting methods. Our analysis shows that clinical trials comprise the largest portion of overall preventive vaccine development costs, a finding in line with other published studies. Clinical phase costs account for around 88 percent of R&D expenditures. Even though our finding on the relative contribution of clinical phase costs to overall R&D expenditures is in line with other published studies, the estimated magnitude of these costs is lower. We find that the clinical phase costs around $105.5 million (20 to 60 percent lower than other published estimates) for preventive vaccines.

The strategy with the largest expected impact on overall development costs is Biomarkers as Surrogate Endpoints (-26.4 percent), followed by Improvements in FDA Review Process Efficiency and Interactions (-14.1 percent), Use of Electronic Health Records (-11.7 percent), and implementation of a Staged Approval Process (-10.6 percent). Those strategies with the lowest expected development cost savings include Reduced SDV (0.4 percent) and CDC/NIH Developing Epidemiological Data on Disease Incidence (0.9 percent).

1 INTRODUCTION

There is ongoing debate on how to spur innovation of new medical products while controlling health care costs. Part of this debate has focused on the rising costs of bringing a medical product to market. Clinical trials constitute a major portion of the overall duration and cost of medical product development.[1] According to published studies (Wilson, 2010; World Health Organization, 2016), the clinical phase of preventive vaccine (PVac) development accounts for between 90 to 95 percent of overall development costs with Phase 3 comprising largest portion of clinical stage costs.

A preventive (also known as prophylactic) vaccine (PVac) is "a biological preparation that stimulates immunity to a particular pathogen. [A PVac] typically contains an agent that resembles a disease-causing microorganism or one of its components often made from weakened or killed forms of the microbe or its toxins. The agent stimulates the body's immune system to recognize it as foreign, destroy it, and remember it, so that the immune system can more easily identify and destroy any of these microorganisms that it encounters later" (The National Academy of Sciences, 2019). Preventive vaccines (e.g., Havrix for prevention of Hepatitis A infection and Vaxchora® for prevention of cholera) are intended to prevent an infection.[2]

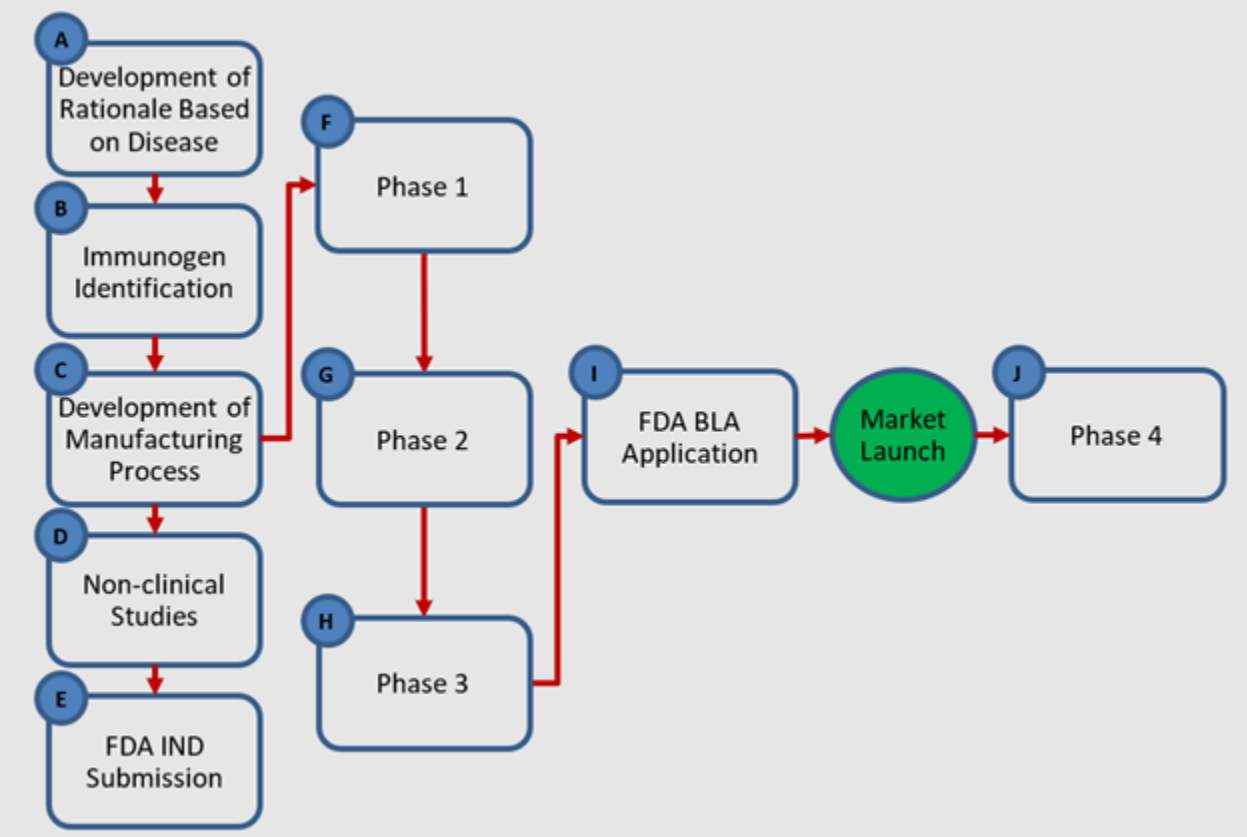
Figure 1 is a simplified diagram of the key events and phases of PVac development in the United States from conception through post-marketing activities (Plotkin, et al., 2018). Overall, development shown in Figure 1 can be broken down into four distinct phases: pre-investigational new drug application (pre-IND) (A—development of rationale based on disease through D—non-clinical studies), pre-marketing/pre-licensure (E—FDA IND Submission through H—Phase 3), licensing (I—FDA BLA application), and post-marketing (J—Phase 4). The early part of the pre-IND phase is characterized by exploratory and laboratory development (A—development of rationale based on disease through C—development of manufacturing process) of one or more vaccine candidates based on a rationale supported by knowledge about the disease (Centers for Disease Control and Prevention, 2014). Later in the pre-IND phase, vaccine candidates undergo nonclinical and preclinical testing for safety and immunogenicity. Toward the end of this phase, the sponsor may request a pre-IND meeting with FDA to obtain non-binding advice on plans to move forward into clinical development with a selected vaccine candidate, as part of the pre-licensure phase. Before clinical testing on human subjects may begin, the sponsor must submit to the FDA an investigational new drug (IND) application with information describing the vaccine's composition and method of manufacture, information summarizing the preclinical, animal, and quality control testing, data demonstrating the vaccine's safety and immunogenicity, and a protocol for the proposed clinical study (Plotkin, et

[1] We acknowledge that strategies for the identification of new compounds (e.g., high-throughput screening, in silico testing, etc.) in early discovery could also have sizable impacts on total development costs. However, such strategies were deemed out of scope for this study given our focus on the clinical research phase.

[2] For the purposes of this analysis, we exclude therapeutic vaccines which are used to bolster immunity to alter the course of a disease (e.g., Provenge® for the treatment of advanced prostate cancer and Imlygic® for the treatment of advanced melanoma).

al., 2018; U.S. Food and Drug Administration, 2018c). FDA reviews all contents of the IND to ensure that study participants of the proposed clinical study would not be exposed to any unacceptable risks. An IND is 'in effect' when the FDA informs the sponsor that the proposed clinical study may proceed. At this point, the sponsor may begin testing on humans under the specified IND number, marking the beginning of the pre-licensure/pre-marketing phase (E—FDA IND Submission through H—Phase 3 in Figure 1).

Figure 1. Overview of Preventive Vaccine Development



Source: Adapted from Plotkin, et al. (2018).

The clinical evaluation of an investigational PVac during the pre-marketing (pre-licensure) phase is typically conducted as a series of separate clinical studies, each generally described in terms of one of three phases. Phase 1 clinical studies test for safety and immunogenicity among a small group (20 to 80) of closely monitored subjects. Phase 2 studies enroll several hundred subjects and provide information on dosing, additional information on safety and immunogenicity, and may assess vaccine activity in a preliminary manner. Phase 3 studies enroll thousands of subjects and provide a thorough assessment on safety and efficacy (Plotkin, et al., 2018; U.S. Food and Drug Administration, 2018c). To support licensure, vaccine efficacy is usually demonstrated through well-controlled randomized and double-blind trials. Occasionally, the sponsor must conduct a large-scale noninferiority study for a new vaccine that is the same general type as a vaccine already on the market (Plotkin, et al., 2018). FDA continues to review study protocols and data submitted to the IND, communicates advice, and

meets with the sponsor at key points throughout this pre-marketing phase, and at any time may halt a study for safety reasons.

Upon completion of clinical trials to support licensure, the sponsor may submit a Biologics License Application (BLA) to FDA's Center for Biologics Evaluation and Research (CBER) for review. The application must demonstrate safety and efficacy, as well as an acceptable manufacturing process, which CBER confirms through a manufacturing facility inspection. CBER may request the FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) to review and comments on the benefit-to-risk ratio of the vaccine. CBER considers VRBPAC's comments before granting licensure, which allows the sponsor to bring the product to the market. Once on the market, the vaccine enters the post-marketing phase (J—Phase 4 in Figure 1), which may include conducting Phase 4 studies to further investigate the duration of immune response to the vaccine or to collect additional safety data. In addition, once a vaccine is licensed, samples and testing protocols for each lot are submitted to FDA for lot-release testing to ensure continued safety, purity, and potency of the PVac product. (Plotkin, et al., 2018; U.S. Food and Drug Administration, 2018c). We estimate the cost of developing a PVac by considering the cost, duration, the probability of successfully transitioning from one stage to the next, and the opportunity cost of capital using the approach by DiMasi, et al. (2016). For the purpose of this analysis, we broke down the overall development of a PVac into six distinct phases, including 1—non-clinical (which includes phases A through E in Figure 1), 2—Phase 1, 3—Phase 2, 4—Phase 3, 5—FDA BLA review, and 6—Phase 4. We acknowledge that there may be some overlap in activities between one phase to the next. Below we present our data sources, model parameters and assumptions, and findings.

Given the relatively large contribution of clinical phase to overall development costs, strategies with potential to reduce time and cost of conducting PVac clinical trials are important. In a previous study, we identified several promising strategies with potential to improve drug development efficiency and hence reduce costs (Eastern Research Group, Inc., 2022). These strategies included:

- **Mobile technologies—**Mobile technologies can include cell phones, wearable trackers, and other devices that capture data directly from patients. Electronic data capture means capturing study data in electronic format. The strategy could entail encouraging the use of mobile and other technologies in clinical trials and the development process as a whole and clarifying requirements around their use.

- **Simplified clinical trial protocols and reduced amendments—**The strategy could entail encouraging sponsors to simplify clinical trial protocols, where possible, ensuring that they have a clear understanding of what is required by FDA and what is superfluous.

- **Reduced source data verification (SDV)—**Source data verification is the process of comparing data collected throughout the clinical trial to the original source of information to verify data integrity. The strategy could entail engaging sponsors in discussions on the topic of data and site monitoring to ensure that they are aware of

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- **Staged approval—**Staged approval could entail granting provisional marketing approval to market a PVac after safety and basic efficacy have been shown, and then continuing to collect additional safety and efficacy data. This would allow the product to be marketed in the United States for use in limited patient populations, and then gradually expand use to additional patient populations as more data to support safety and efficacy in those populations are collected.

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2 STUDY OBJECTIVE

The primary aim of this study is to evaluate the potential savings from implementing the strategies identified above. To facilitate this evaluation, an analytical model that accounts for the cost, duration, the probability of successfully transitioning from one development stage to the next depicted in Figure 1 is needed. Thus, our secondary objective is the development of such a model using public and private data sources.

3 ANALYTICAL FRAMEWORK

To be able to assess the impact of clinical trial strategies noted in Section 1 above on development costs, we first need estimates of baseline development costs for PVacs. We use the method by DiMasi et al. (2016; 1991) that takes account of the cost of failures and cost of capital. The methodology is described in detail in DiMasi et al. (1991); thus, we only summarize it below.

PVac development progresses in phases from early research and development to animal testing, to testing in humans, to regulatory submission for marketing approval and to post-approval studies. For the purpose of this analysis, we broke down the overall development of a PVac as shown in Figure 1, into six distinct phases, including 1—non-clinical, which includes all steps in between target discovery (Stage A) and FDA IND approval (Stage F), 2—Phase 1, 3—Phase 2, 4—Phase 3, 5—FDA review, and 6—Phase 4. If the cash outlay (also known as out-of-pocket cost) associated with a given phase i is C_i, then the expected cost, $E(C_i)$, that incorporates failures can be computed by dividing this cost by the transition success probability from phase i to launch, p_i, i.e.,

$$E(C_i) = \frac{C_i}{p_i} \quad (1)$$

Assuming that phase costs are distributed uniformly over the length of the phase, t_i, the capitalized cost, CC_i, that accounts for the opportunity cost of the investment in the PVac is given by:

$$CC_i = \int_{t_{i,e}}^{t_{i,b}} \left(\frac{C_i}{t_i}\right)(e^{rt})dt \tag{2}$$

where r is the cost of capital that captures the time value effect; $t_{i,b}$ is the time from the beginning, b, of the given phase to product launch, and $t_{i,e}$ is the time from the end, e, of the given phase to product launch. The above equation then becomes:

$$CC_i = \frac{C_i/t_i}{r}(e^{rt_{i,b}} - e^{rt_{i,e}}) \tag{3}$$

Given the above equations, we can then compute the expected capitalized cost of phase i that accounts for the cost of failures as well as the cost of capital as:

$$E(CC_i) = \frac{CC_i}{p_i} \tag{4}$$

Then the total expected capitalized cost of development for a PVac, $E(CC)$, is the sum of the expected capitalized cost of each phase i,

$$E(CC_i) = \sum_{i=1}^{n} E(CC_i) \tag{5}$$

where i = non-clinical, Phase 1, Phase 2, Phase 3, FDA review, and Phase 4.

For example, suppose the total out of pocket cash outlay for Phase 2 is $5 million for a given PVac x and the probability of p making it to market given that it is in Phase 2 is 40 percent, then the expected cost of Phase 2, $E(C_2)$, that accounts for failures is $12.5 million, i.e.,

$$E(C_2) = \frac{C_2}{p_2} = \frac{\$5{,}000{,}000}{0.40} = \$12{,}500{,}000 \tag{6}$$

If we further assume that the cost of capital, r, is 1 percent per month (i.e., 12 percent per annum) and that Phase 2 lasts 35 months (t_2 = 35) begins 105 months before drug launch (t_2^b = 105) and ends 71 months before drug launch (t_2^e = 71) then the capitalized cost of Phase 2, CC_2, that accounts for the opportunity cost of the investment in PVac x is $11.8 million, i.e.,

$$CC_2 = \frac{C_2/t_2}{r}(e^{rt_{2,b}} - e^{rt_{2,e}}) = \frac{\$5{,}000{,}000/35}{0.01}(e^{0.01\times105} - e^{0.01\times71}) = \$11{,}766{,}569 \tag{7}$$

Using the above equations, we can compute the expected capitalized cost of Phase 2, $E(CC_2)$, as $29.4 million:

$$E(CC_2) = \frac{CC_2}{p_2} = \frac{\$11{,}766{,}569}{0.40} = \$29{,}416{,}423 \quad (8)$$

We use this approach to compute the total expected capitalized cost of developing a PVac as described in the sections below.

4 DATA SOURCES

As of November 2019, there were a total of 82 vaccines licensed for use in the United States (U.S. Food and Drug Administration, 2019a). For this model, we selected 14 out of the 82 approved vaccines, which we refer to as our CBER vaccine sample. For each of the vaccines in the sample we compiled clinical trial related data (Table 1), such as number of patients enrolled and study duration. We considered whether a vaccine was new (recently approved) and/or novel,[3] deemed important by Plotkin, et al. (2018), and suggested for inclusion by the project advisory group assembled for this study in selecting our vaccine cohort. We also narrowed our selection of vaccines by focusing on those that were approved for marketing in the U.S. on or after 2000 and for which FDA submission information was readily available from public sources.

Table 1. FDA CBER Vaccine Sample

Product Name	Trade Name
Cholera Vaccine Live Oral	Vaxchora
Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant	Gardasil
Zoster Vaccine, Live, (Oka/Merck)	Zostavax
Zoster Vaccine Recombinant, Adjuvanted	Shingrix
Hepatitis B Vaccine (Recombinant), Adjuvanted	HEPLISAV-B
Human Papillomavirus Bivalent (Types 16, 18) Vaccine, Recombinant	Cervarix
Japanese Encephalitis Virus Vaccine, Inactivated, Adsorbed	Ixiaro
Meningococcal Group B Vaccine	BEXSERO
Meningococcal Group B Vaccine	TRUMENBA
Rotavirus Vaccine, Live, Oral	ROTARIX
Rotavirus Vaccine, Live, Oral, Pentavalent	RotaTeq
Human Papillomavirus 9-valent Vaccine, Recombinant	Gardasil 9
Meningococcal (Groups A, C, Y & W-135) Polysaccharide Diphtheria Toxoid Conjugate Vaccine	Menactra
Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)	Prevnar 13

Source: U.S. Food and Drug Administration, (2019a)

For each of the vaccines selected, we identified those clinical trials conducted to support the BLA and available information related to the pre-IND activities, such as the date of IND

[3] The term 'novel' is ambiguous. For example, the 4 valent HPV vaccine might have been considered 'novel' at time of approval. However, the 9 valent HPV vaccine would no longer be considered 'novel' in design since it is predicated on the 4 -valent vaccine.

submission to the FDA noted in the publicly available FDA communications and the date a patent was filed for the vaccine compound by reviewing the following sources:

- FDA BLA approval letters, BLA clinical review documents, and FDA-approved package inserts available on the FDA CBER website (U.S. Food and Drug Administration, 2021e; U.S. Food and Drug Administration, 2017; U.S. Food and Drug Administration, 2019a),
- FDA Vaccines and Related Biological Products Advisory Committee (VRBPAC) presentations (U.S. Food and Drug Administration, 2021f),
- Registered trials on clinicaltrials.gov,
- Citeline – Pharmaprojects information on clinical development history, and
- PubChem and U.S. Patent and Trademark Office (USPTO) information on patents granted.

In addition to the above data sources, we also used published studies and expert opinion to support our parameter estimates and assumptions as described in those sections below, where applicable.

5 MODEL PARAMETERS AND ASSUMPTIONS

Table 2 presents the parameter estimates and assumptions for our PVac development cost model. The following sections discuss the basis for these estimates.

Table 2. Summary of Preventive Vaccine Development Cost Model Parameters and Assumptions

Parameter	Phase	Value	Source
Phase Durations (in months)	Non-clinical	64.4	Published studies; CBER vaccine sample; expert opinion
	Phase 1	29.2	
	Phase 2	36.4	
	Phase 3	45.4	
	FDA BLA review	15.1	
	Phase 4	58.6	
Start to Start (in Months)	Non-clinical to phase 1	64.4	Published studies
	Phase 1 to Phase 2	14.6	CBER vaccine sample
	Phase 2 to Phase 3	36.0	
	Phase 3 to FDA BLA review	53.6	
	FDA BLA review to approval	15.1	Published studies; CBER vaccine sample
Out of Pocket Phase Costs (in $ 2018)	Non-clinical	$11,841,009	Published studies
	Phase 1	$5,673,733	Calculation
	Phase 2	$12,782,945	Calculation
	Phase 3	$86,994,393	Calculation
	FDA BLA review	$2,057,912	Published studies
	Phase 4	$13,362,423	Cutting Edge Information, LLC (2013); CBER vaccine sample

Parameter	Phase	Value	Source
Average Number of Total Patients Enrolled	Non-clinical	NA	Not applicable
	Phase 1	149	CBER vaccine sample
	Phase 2	3,911	CBER vaccine sample
	Phase 3	23,179	CBER vaccine sample
	FDA BLA review	NA	Not applicable
	Phase 4	12,794	CBER vaccine sample
Average Per-patient Costs (in $ 2018)	Non-clinical	NA	Not applicable
	Phase 1	$38,130	Published studies; CBER vaccine sample
	Phase 2	$3,268	
	Phase 3	$3,753	
	FDA BLA review	NA	Not applicable
	Phase 4	$1,044	Calculation
Transition Success Probabilities (%)	Non-clinical to phase 1	44.4%	Published studies; expert opinion
	Phase 1 to Phase 2	64.6%	
	Phase 2 to Phase 3	45.8%	
	Phase 3 to FDA BLA review	75.9%	
	FDA BLA review to approval	94.2%	
Cost of Capital (%)		11.0%	Published studies

5.1 PHASE DURATIONS

The phase duration parameter refers to the time it takes to complete a given phase of development depicted in Figure 1. For the non-clinical phase, our estimate represents the time it takes for exploratory research; laboratory development of vaccine candidates; preclinical testing of the vaccine candidates for safety and immunogenicity; and original submission of an IND, which is required by FDA to begin testing in human subjects.[4] We used published studies, expert opinion, and information compiled on the CBER vaccine sample to estimate average phase durations across all development stages (Table 3). From Table 3, the non-clinical phase is the longest (64.4 months) stage of PVac development followed by post-approval study phase (i.e., Phase 4) (58.6 months), Phase 3 (45.4 months), and Phase 2 (36.4 months). The average time for FDA review and approval of a BLA for a PVac is 15.1 months.

5.2 TIME FROM PHASE START TO NEXT PHASE START

The start-to-start parameter refers to the elapsed time between the start of one development phase (e.g., Phase 2) supporting a BLA and the start of the next development phase (e.g., Phase 3) supporting the same application. For the non-clinical phase to Phase 1 estimate, we assumed that Phase 1 will begin immediately upon successful completion of the non-clinical development phase and notification from FDA that the proposed Phase 1 study in the submitted IND may proceed, (i.e., when the IND is in effect) as per 21 CFR 312.20 (b) and 21

[4] Submission of an IND which is essentially a request to begin testing of an investigational vaccine in humans per a submitted study protocol, would occur at the end of the pre-IND phase. Once the proposed study in the original IND is allowed to proceed based on review of information including the proposed study protocol in the IND, the next phase, the pre-licensure phase (focused on clinical development and accompanied by continued manufacturing development) begins. This next phase would begin once the submitted IND is "in effect."

CFR 312.40. Similarly, for the FDA BLA submission to approval estimate, we used 15.1 months as estimated in Table 3.

Similar to the drug development process, for a PVac, work may also overlap with some of the clinical phases. In other words, the sponsor may begin one or more Phase 2 clinical trials before completing Phase 1 clinical trials. To estimate the average phase start to next phase start durations (Table 4) we used our CBER vaccine sample. For each of the 14 vaccines, we computed the difference between the earliest reported Phase 1 study start and the earliest reported Phase 2 study start dates; the earliest reported Phase 2 study start and the earliest reported Phase 3 study start dates; and the earliest reported Phase 3 study start and the FDA BLA submission dates.

Table 3. Average Phase Durations (in Months)

Source	Non-clinical	Phase 1	Phase 2	Phase 3	FDA Review	Phase 4
Chit, et al. (2014)	NA	21.0	21.0	46.0	NA	NA
Davis, et al. (2011)	44.3	34.5	47.4	45.0	NA	NA
Expert Opinion [a]	21.4	23.5	34.0	49.0	15.0	48.0
CBER Vaccine Sample	173.9 [b]	43.3	54.4	74.3	15.6	98.4
Pronker, et al. (2013)	18.0	29.7	34.2	31.6	14.9	NA
Wong, et al. (2019)	NA	23.4	27.1	26.2	NA	29.5
Average	**64.4**	**29.2**	**36.4**	**45.4**	**15.1**	**58.6**

NA = Not available

[a] Represents the average of non-clinical phase duration estimates provided by our expert panel.

[b] Following the methodology by Beall, et al. (2019), we used the difference between the date of IND submission to FDA and the date for initial patent filing with the USPTO as a proxy for the non-clinical phase duration for each of the 14 vaccines in our CBER vaccine sample (see Section 4). The reported figure represents the average across those vaccines included in our sample for which we were able to identify IND and patent filing dates (10 out of 14 vaccines).

Table 4. Stage Start to Next Stage Start Durations (in Months) for Vaccines Selected for Analysis

Vaccine Name	Phase 1 Start to Phase 2 Start	Phase 2 Start to Phase 3 Start	Phase 3 Start to FDA Review	FDA BLA Review to Approval [a]
Vaxchora	25.7	NA	25.0	7.8
Gardasil	12.6	19.4	66.3	6.0
Zostavax	15.1	8.7	76.8	13.7
Shingrix	26.0	41.4	74.5	11.9
HEPLISAV-B	20.2	34.2	82.0	66.3
Cervarix	8.6	54.1	34.7	30.6
Ixiaro	NA	NA	26.9	15.9
BEXSERO	16.9	8.0	76.6	6.0
TRUMENBA	3.4	98.2	NA	4.4
ROTARIX	NA	35.4	45.9	10.0
RotaTeq	NA	NA	50.7	9.9
Gardasil 9	NA	NA	NA	12.0
Menactra	NA	NA	NA	12.9
Prevnar 13	3.0	24.5	30.3	10.8

Vaccine Name	Phase 1 Start to Phase 2 Start	Phase 2 Start to Phase 3 Start	Phase 3 Start to FDA Review	FDA BLA Review to Approval [a]
Average	**14.6**	**36.0**	**53.6**	**15.6**

NA = Not available

[a] There are several factors that may extend the overall review time as presented here, such as if a Complete Response letter is sent to the sponsor and if a major amendment is submitted. Further, some of the vaccines were reviewed on a priority review clock and an approval action was made on or by the action due date. Others were reviewed on a standard review clock.

Table 3 and Table 4 show that there is overlap between successive stages of clinical development. For example, sponsors begin Phase 2 studies on a larger cohort of healthy volunteers with more diverse conditions when initial immunogenicity and toxicity results from Phase 1 studies are available even if those studies may not be fully complete. Thus, even though a Phase 1 study is estimated to last around 29.2 months (Table 3) on average, a sponsor may begin a Phase 2 study 14.6 months (Table 4) after initiating the associated Phase 1 study.

It should be pointed out that even though we report the FDA BLA review and approval times for each vaccine in the CBER vaccine sample, we combined the group average for the 14 vaccines (15.6 months) with the estimate reported in Pronker, et al. (2013) (14.9 months) and that by our expert panel (15.0 months) in the model to increase the sample size (see Table 3).

5.3 OUT-OF-POCKET COSTS BY PHASE OF DEVELOPMENT

The out-of-pocket cost parameter represents the average out-of-pocket expenses (not adjusted for failures or cost of capital) a sponsor incurs during a given PVac development phase. These development costs vary considerably based on vaccine type, innovation level, and disease target (Plotkin, et al., 2017). Additionally, sectoral affiliation (commercial versus non-commercial; public versus private), track record of the sponsor, and platform technology (e.g., attenuated virus-based, inactivated pathogen-based, sub-unit protein based, nucleic acid-based, peptide-based, and viral vector-based) all impact development costs (Gouglas, et al., 2018).

Table 5 presents cost estimates by stage of development obtained from published literature in the vaccine space. The studies drew on development data from vaccines that targeted a wide range of pathogens such as WHO prioritized severe outbreak pathogens[5] (Gouglas, et al., 2018; World Health Organization, 2016) or seasonal influenza (Chit, et al., 2014). In all cases where data are available, Phase 3 is the costliest development phase with out-of-pocket expenditure ranging from $60 million to over $148 million (Table 5) during which the sponsor continues to monitor the vaccine's toxicity, immunogenicity, and serious adverse events. Phase 1, in which sponsors test safety and immunogenicity is the least costly

[5] The 11 pathogens WHO prioritized that may lead to severe outbreaks in the future include: Crimean Congo haemorrhagic fever, chikungunya, Ebola, Lassa, Marburg, Middle East respiratory syndrome coronavirus, Nipah, Rift Valley fever, severe acute respiratory syndrome, severe fever with thrombocytopenia syndrome, and Zika virus (Gouglas, et al., 2018; World Health Organization, 2016)

development stage at an average of $6.5 million while the average non-clinical phase ($13.8 million), Phase 2 ($14.6 million), and Phase 4 ($13.4 million) costs are comparable.

WHO defines simple vaccines as those that build off of previous technologies or platforms that have been used to develop other vaccines, and complex vaccines as those that apply a completely novel approach as they do not have existing research or platforms (World Health Organization, 2016). For each stage of development, the costs of complex vaccines are greater than those of simple vaccines as reported by WHO (2016), but the difference is greatest for the non-clinical phase, which reflects the extensive early-stage research required for novel complex vaccines.

Table 5. Published Estimates of Out-of-pocket Costs (in 2018 $ Million) by Development Stage

Source	Type	Non-clinical	Phase 1	Phase 2	Phase 3	FDA BLA Review	Phase 4
Gouglas et al, (2018)	High	$26.28	$14.21	$28.00	NA	NA	NA
	Low	$7.88	$6.81	$16.78	NA	NA	NA
World Health Organization (2016)	Simple	$6.91	$2.27	$13.61	$114.58	NA	NA
	Complex	$17.12	$2.58	$14.34	$137.48	NA	NA
Wilson (2010)	Low	$6.17	$4.94	$4.94	$61.74	$2.47	NA
	High	$18.52	$12.35	$12.35	$148.17	$3.70	NA
Chit et al., (2014) [a]	Seasonal influenza	NA	$2.24	$12.25	$60.00	NA	NA
Cutting Edge (2013) and CBER Vaccine Sample [b]	All	NA	NA	NA	NA	NA	$13.36
Average		**$13.81**	**$6.48**	**$14.61**	**$104.39**	**$3.09**	**$13.36**

NA = Not available/Not applicable

[a] The reported values in Chit et al. (2014) were in 2010 Canadian dollars. We converted them to 2018 US dollars here.

[b] Represents the product of the average cost of four Phase 4 vaccine trials in immunology reported in Cutting Edge (2013) and the average number of Phase 4 studies per vaccine estimated from the CBER vaccine sample (see Table 6).

Along with the many other factors described above, trial size may also impact the cost of a development stage. Table 6 presents the number of studies, total number of patients, and average number of patients per study for Phase 1 through 4 trials for the FDA CBER vaccine sample. These vaccines do not fully align with those used to develop the cost estimates in Table 5, but the data reveal trends in the size of each stage. Phase 3, the costliest development stage (Table 5), also has the highest average number of total patients, 23,179, and highest average number of patients per study, 4,490 for the vaccines in the FDA CBER vaccine sample (Table 6). On the other hand, Phase 1 is often a less expensive PVac development stage than Phase 3, with an average number of 149 total patients and an average number of 80 patients per study.

Based on these estimates, we calculated the average out of pocket costs across the 14 PVacs in our sample for Phases 1 through 3 as:

$$C_i = CPP_i \times n_i \quad (9)$$

where CPP is the average cost per patient for a Phase i clinical trial (i = 1, 2, and 3) (Section 5.4), and n is the total number of patients enrolled for the same phase (Table 6). To calculate Phase 4 out of pocket costs, we relied on the total per Phase 4 clinical study costs ($3,485,849 in $ 2018) calculated from data reported in Cutting Edge Information, LLC (2013) and the average number of Phase 4 clinical trial studies (4 as reported in Table 6) conducted for the PVacs in our CBER vaccine sample, i.e.:

$$C_4 = CS_4 \times N_4 \quad (10)$$

where C_4 is the total Phase 4 clinical study cost and N_4 is the average number of clinical studies conducted for Phase 4.

Table 6. Number of Studies, Total Number of Patients, and Average Number of Patients per Study, by Development Stage in the FDA CBER Vaccine Sample

Vaccine Name	Parameter	Phase 1	Phase 2	Phase 3	Phase 4
Vaxchora	Number of Studies	1	1	3	1
	Total Number of Patients	66	150	3,741	595
	Average Number of Patients per Study	66	150	1,247	595
Gardasil	Number of Studies	3	2	7	5
	Total Number of Patients	289	2,889	29,285	2,161
	Average Number of Patients per Study	96	1,445	4,184	432
Zostavax	Number of Studies	1	4	6	4
	Total Number of Patients	276	795	62,998	12,285
	Average Number of Patients per Study	276	199	10,500	3,071
Shingrix	Number of Studies	4	2	7	NA
	Total Number of Patients	418	1,125	32,965	NA
	Average Number of Patients per Study	105	563	4,709	NA
HEPLISAV-B	Number of Studies	3	4	4	NA
	Total Number of Patients	126	461	13,491	NA
	Average Number of Patients per Study	42	115	3,373	NA
Cervarix	Number of Studies	2	4	6	3
	Total Number of Patients	80	1,836	30,500	38,474
	Average Number of Patients per Study	40	459	5,083	12,825
Ixiaro	Number of Studies	1	1	7	2
	Total Number of Patients	25	24	8,394	264
	Average Number of Patients per Study	25	24	1,199	132
BEXSERO	Number of Studies	1	4	4	3
	Total Number of Patients	70	3,678	5,263	3,536
	Average Number of Patients per Study	70	920	1,316	1,179
TRUMENBA	Number of Studies	2	5	1	1
	Total Number of Patients	108	5,519	1,590	18
	Average Number of Patients per Study	54	1,104	1,590	18
ROTARIX	Number of Studies	NA	6	5	3
	Total Number of Patients	NA	6,374	25,951	991
	Average Number of Patients per Study	NA	1,062	5,190	330
RotaTeq	Number of Studies	NA	NA	4	2
	Total Number of Patients	NA	NA	72,132	258

Vaccine Name	Parameter	Phase 1	Phase 2	Phase 3	Phase 4
	Average Number of Patients per Study	NA	NA	18,033	129
Gardasil 9	Number of Studies	NA	1	5	5
	Total Number of Patients	NA	15,457	6,818	506
	Average Number of Patients per Study	NA	15,457	1,364	101
Menactra	Number of Studies	NA	6	NA	6
	Total Number of Patients	NA	12,292	NA	4,758
	Average Number of Patients per Study	NA	2,049	NA	793
Prevnar 13	Number of Studies	1	1	14	11
	Total Number of Patients	30	249	8,196	89,680
	Average Number of Patients per Study	30	249	585	8,153
Average Number of Studies		**2**	**3**	**6**	**4**
Average Number of Total Patients		**149**	**3,911**	**23,179**	**12,794**
Average Number of Patients per Study		**80**	**1,830**	**4,490**	**2,313**

NA = Not available

5.4 AVERAGE PER-PATIENT COSTS

The per-patient cost parameter represents the average cost a sponsor incurs per-patient in a clinical trial study supporting a BLA application. We estimated the average per-patient cost by dividing the total out-of-pocket stage cost reported in Table 5 by the average number of total patients estimated in Table 6. This method yielded an average per-patients cost of $38,130 for Phase 1, $3,268 for Phase 2, $3,753 for Phase 3, and $1,044 for Phase 4.

5.5 PHASE TRANSITION SUCCESS PROBABILITIES

The phase transition success probability parameter represents the probability of a sponsor successfully moving from one stage of PVac development depicted in Figure 1 to the next. If, for example, out of 100 PVacs that make it to Phase 1, 30 successfully proceed to Phase 2, then the phase transition probability from Phase 1 to Phase 2 is 30 percent.

We used published studies combined with expert opinion to estimate the average phase transition success probabilities as shown in Table 7 below. Successfully transitioning from non-clinical development to Phase 1 and then from Phase 2 to Phase 3 has the lowest likelihood at 44.4 percent and 45.8 percent, respectively. The likelihood of successfully moving from Phase 1 to Phase 2 as well as from Phase 3 to the FDA review phase stage is higher at 64.6 percent and 75.9 percent, respectively. The likelihood of FDA approval of a preventive vaccine that has made it through Phase 3 is 94.2 percent.

Table 7. Phase Transition Success Probabilities for Preventive Vaccines

Source	Type	Non-clinical to Phase 1	Phase 1 to Phase 2	Phase 2 to Phase 3	Phase 3 to FDA Review	FDA Review to Approval
BiomedTracker (2016)	All	NA	66.3%	32.9%	74.3%	100.0%
Chit et al (2014)	Seasonal influenza	NA	40.0%	74.0%	69.0%	NA
Davis, et al. (2011)	All	48.0%	74.0%	58.0%	NA	NA
Expert Opinion	All	55.0%	51.3%	37.5%	75.0%	91.8%

Source	Type	Non-clinical to Phase 1	Phase 1 to Phase 2	Phase 2 to Phase 3	Phase 3 to FDA Review	FDA Review to Approval
Lo et al (2020)	Industry sponsored	NA	82.5%	65.4%	NA	NA
	Non-industry sponsored	NA	63.3%	37.3%	NA	NA
Pronker et al (2013)	All	41.2%	81.0%	31.3%	78.8%	85.0%
World Health Organization (2016)	Simple	41.0%	68.0%	46.0%	71.0%	NA
	Complex	41.0%	50.0%	22.0%	64.0%	NA
Wilson (2010)	All	40.0%	33.0%	33.0%	75.0%	NA
Wong et al (2019)	All	NA	76.8%	58.2%	NA	NA
	Orphan only	NA	89.5%	53.5%	100.0%	100.0%
Average [a]		**44.4%**	**64.6%**	**45.8%**	**75.9%**	**94.2%**

NA = Not available

[a] Represents the simple average of all reported values in the column.

Overall, only 9.4 percent (= 0.444 × 0.646 × 0.458× 0.759 × 0.942) of PVac candidates successfully move from non-clinical development to market. However, as the vaccine candidate successfully clears each successive development stage, the odds of making it to market improve.

5.6 OPPORTUNITY COST OF CAPITAL

The opportunity cost of capital (OCOC) represents the rate of return (net of inflation) that the sponsor would otherwise be able to earn at the same risk level as the investment in the new drug that has been selected. Some critics have argued that "innovative companies must do R&D, and this is a regular cost of doing business; so estimated profits foregone should not be added to out-of-pocket costs. If revenues are coming in from other products, then the [R&D] costs are recovered as one goes along" (Light & Warburton, 2011). Others have questioned whether the appropriate cost of capital should be as high as 11 percent, the value used in several studies from the Tufts Center for the Study of Drug Development (Tufts CSDD).

As described by Chit, et al. (2015), there is an opportunity cost associated with the use of capital, which is a scarce resource, and this cost needs to be accounted for in estimating drug development costs. The value of OCOC can vary significantly by sponsor-specific factors, such as product portfolio, venture capital funding, and size of company, as well as other exogenous factors, such as economic and regulatory climate for drug development projects. There are accepted methods in finance for estimating the opportunity cost of capital for different economic sectors and firms, including the capital asset pricing model (CAPM), and the Fama and French (F-F) 3-factor model. The CAPM model is the most widely used approach (Chit, et al., 2015).

There are numerous CAPM studies that evaluated OCOC for the biopharmaceutical market as a whole as well as some broad sub-sectors, such as small and large molecules. Table 8 presents the different OCOC estimates available from the published literature. There are, however, no published studies that estimate OCOC for vaccines specifically. Thus, we used 11

percent as the OCOC for PVac development projects, which is the average of figures reported for the biopharmaceutical industry as a whole depicted in Table 8.

Table 8. Published Estimates of Opportunity Cost of Capital

Data Source	Sub-Sector	Firm Size	Study Period	Sample Size	Opportunity Cost of Capital
DiMasi et al, (2016)	All	All	2000	NA	11.8%
			2005	NA	10.8%
			2010	NA	9.4%
DiMasi et al, (2003)	All	All	2000	NA	11.9%
Damodaran, (2018)	Large Molecule	All	2018	459	9.2%
	Small Molecule	All	2018	185	8.1%
Damodaran, (2019)	Large Molecule	All	2019	481	10.5%
	Small Molecule	All	2019	237	10.5%
Paul et al, (2010)	All	All	2007	NA	11.0%
Harrington, (2012)	Small Molecule	All	2001-2005	31	9.8%
		Large	2001-2005	22	9.6%
		Small	2001-2005	9	10.6%
	Large Molecule	All	2001-2005	26	14.2%
		Large	2001-2005	17	14.1%
		Small	2001-2005	9	14.5%
	Small Molecule	All	2006-2008	28	9.3%
		Large	2006-2008	21	9.5%
		Small	2006-2008	7	8.6%
	Large Molecule	All	2006-2008	29	11.8%
		Large	2006-2008	14	10.2%
		Small	2006-2008	15	13.2%
Average	**Large Molecule**	**Large**			**12.2%**
		Small			**13.9%**
		All			**11.4%**
	Small Molecule	**Large**			**9.6%**
		Small			**9.6%**
		All			**9.4%**
	All	**Large**			**NA**
		Small			**NA**
		All [a]			**11.0%**

NA = Not available

[a] Estimate used in this model.

6 RESULTS

6.1 BASELINE DEVELOPMENT COST ESTIMATES

Our analysis suggests that the average out-of-pocket cost of developing a PVac is around $119.3 million before conducting post-approval studies, and approximately $132.7 million when post-approval studies are accounted for (see Table 9). Of those costs exclusive of post-approval studies, 10 percent is non-clinical stage related, 88 percent is clinical stage (i.e., Phase 1, 2, and 3) related, and the remaining 2 percent is associated with the FDA review phase.

When capitalized to account for the time value of money and after accounting for the costs of failures, expected capitalized average development cost for PVac development is approximately $876.4 million before conducting post-approval studies and $886.8 million after conducting them. As indicated, capitalized costs are higher than out-of-pocket costs because they take into account the opportunity cost of capital that embodies the time value of money as well as the fact that there will be failures along the way. These figures represent our baseline cost of PVac development against which we evaluate different strategies (see Table 10) designed to improve likelihood of phase transition success and/or reduce non-clinical, clinical, FDA review, and Phase 4 related costs and durations.

As Table 9 illustrates, the primary driver of development cost is non-clinical stage expenditures when we account for cost of failures and opportunity cost of capital. From a capitalized out-of-pocket cost perspective that takes account of the time value of the investment but not failure costs, the non-clinical development phase accounts for over 20 percent of total capitalized development costs, regardless of post-approval costs. From an expected capitalized cost perspective in which both cost of failures and the time value of the investment are incorporated, the share of total expected development cost represented by the non-clinical phase is 58 percent, exclusive of post-approval costs. The non-clinical phase represents the largest portion of total expected capitalized development costs primarily because the probability of moving from the non-clinical phase to a marketable PVac is only 9.4 percent.[6] Thus, the $11.8 million and nearly 6 years needed to conduct non-clinical studies are much greater in real economic impact than their nominal value suggests.

[6] Multiplying together all the phase transition success probabilities listed in Table 7 (i.e., successfully moving from non-clinical phase to FDA marketing approval), results in a product of 9.4 percent.

Table 9. Average Cost of Developing a Preventive Vaccine for the U.S. Market (in Million $ 2018)

Development Stage	Transition Success Probability [a]	Out-of-Pocket Costs (in $ 2018) [b]		Expected Out-of-Pocket Costs (in $ 2018) [c]		Capitalized Out-of-pocket Costs to Date of Launch (in $ 2018) [d]		Expected Capitalized Out-of-pocket Costs (in $ 2018) [e]	
		$	%	$	%	$	%	$	%
Non-clinical Phase	9.4%	$11.8	10%	$126.2	38%	$48.1	21%	$512.6	58%
Clinical Phases	NA	$105.5	88%	$187.6	56%	$176.8	78%	$343.7	39%
Phase 1 [f]	21.1%	$5.7	5%	$26.8	8%	$14.8	7%	$70.2	8%
Phase 2 [f]	32.7%	$12.8	11%	$39.1	12%	$28.4	12%	$86.7	10%
Phase 3 [f]	71.5%	$87.0	73%	$121.7	37%	$133.6	59%	$186.9	21%
FDA Review	94.2%	$2.1	2%	$18.7	6%	$2.2	1%	$20.1	2%
Phase 4 [g]	NA	$13.4	NA	$13.4	NA	$10.3	NA	$10.3	NA
Total (without Phase 4 costs)	**NA**	**$119.3**	**100%**	**$332.6**	**100%**	**$227.0**	**100%**	**$876.4**	**100%**
Total (with Phase 4 costs)	**NA**	**$132.7**	**NA**	**$346.0**	**NA**	**$237.4**	**NA**	**$886.8**	**NA**

NA = Not applicable

Figures may not add up due to rounding.

[a] The figure represents the transition probability from the given stage to approval.

[b] These are the raw out-of-pocket expenses not adjusted for cost of capital or failures.

[c] The figures represent the out-of-pocket expenses after adjusting for the cost of failures computed as the raw out-of-pocket cost divided by the transition success probability. Expected out-of-pocket costs take into account the costs of failures but not the time value of the investment.

[d] The figures represent the out-of-pocket costs at the point of launch after adjusting for the time value of the investment; computed in accordance with approach described in Section 3. Capitalized out-of-pocket costs take into account the time value of the investment but not the costs of failures.

[e] Expected capitalized costs take into account the costs of failures and the time value of money.

[f] The out-of-pocket cost is estimates as the product of average cost per patient and the total number of patients for that phase.

[g] See Section 5.3 for a description of how out-of-pocket costs are estimated for Phase 4.

As the developer successfully transitions from one development stage to another, the likelihood of approval, hence expected returns change. Even though a large, Phase 3 study may be more expensive out-of-pocket than non-clinical work (i.e., development of rationale, immunogen identification, manufacturing process development, non-clinical/preclinical studies, and submission of an FDA IND with plans to begin human trials), the odds of a PVac candidate making it to market is significantly higher (71.5 percent) if the PVac candidate has already cleared the non-clinical, Phase 1, and Phase 2 stages than one that is at the immunogen identification stage (9.4 percent).

The clinical phases of PVac development (Phase 1, 2, and 3) also contribute substantially to total out of pocket development costs, comprising around 88 percent of total costs. From a capitalized out-of-pocket cost perspective, clinical development comprises 78 percent of total capitalized development costs, excluding post-approval costs but including the time value of the investment. From an expected capitalized out-of-pocket cost perspective, the share of total expected capitalized development costs represented by clinical development is around 39 percent, excluding post-approval costs. Phase 3 costs constitute the vast majority of clinical development costs, due primarily to enrolling large number of patients (approximately 23,000 versus 150 for Phase 1), taking significantly longer than Phase 1 (45.4 months versus 29.2 months), and greater out-of-pocket costs (approximately $87.0 million vs. $5.7 million).

6.2 IMPACT OF SELECT CLINICAL TRIAL STRATEGIES ON THE TOTAL COST OF PREVENTIVE VACCINE DEVELOPMENT

As described in our previous study (Eastern Research Group, Inc., 2022), we asked our panel of vaccine experts to evaluate the impact of various clinical study strategies on the cost, duration, and phase transition success probability of PVac development stages. A summary of our experts' estimates is presented in Table 10. Negative percentages indicate reductions in a given parameter (e.g., use of mobile technologies would *reduce* clinical study costs, on average, by 3 percent during Phase 1), and positive percentages indicate increases in a given parameter (e.g., using biomarkers as surrogate endpoints would *increase* a developer's probability of successfully transitioning from Phase 2 to Phase 3, on average, by 7 percent).

We then evaluated the overall impact of each strategy on total expected development cost (see Table 11). Using our total expected capitalized cost (including post-approval studies) of $886.8 million as our baseline, we evaluated the change (or delta [Δ]) to this total expected cost if a developer were to implement a given strategy. For each strategy, we evaluated the reduction in overall expected development cost attributable to the cost savings, time savings, and increases in phase transition success probability associated with that strategy. For example, use of adaptive design in clinical trial protocols are associated with sponsor overall cost savings of 0.5 percent, time savings of 2.4 percent, and a phase transition success probability increase of 0.6 percent (Table 11). When incorporated into our PVac development cost model, these changes result in a total expected development cost of $855.3 million, which is approximately 1.5 percent lower than our baseline estimate of $886.8 million.

Table 10. Expert Estimates of Strategy Impacts on Cost, Duration, and Probability of Phase Transition Success for Preventive Vaccines

Element	Phase	Cost	Duration	Success Likelihood
Mobile Technologies	Non-clinical	0%	0%	0%
	Phase 1	-3%	-1%	0%
	Phase 2	-6%	-4%	0%
	Phase 3	-8%	-6%	0%
	FDA Review	0%	0%	1%
	Phase 4	-9%	-8%	NA
Simplified Clinical Trial Protocols and Reduced Amendments	Non-clinical	0%	0%	0%
	Phase 1	-1%	-1%	0%
	Phase 2	-5%	-5%	0%
	Phase 3	-10%	-7%	0%
	FDA Review	0%	-1%	0%
	Phase 4	-7%	-5%	NA
Reduced SDV	Non-clinical	0%	0%	0%
	Phase 1	-1%	0%	0%
	Phase 2	-1%	0%	0%
	Phase 3	-1%	0%	0%
	FDA Review	0%	0%	0%
	Phase 4	0%	0%	NA
Improvements in FDA Review Efficiency and Interactions	Non-clinical	0%	0%	0%
	Phase 1	0%	-2%	3%
	Phase 2	0%	-2%	5%
	Phase 3	0%	-2%	8%
	FDA Review	-1%	-5%	0%
	Phase 4	0%	-2%	NA
Staged Approval	Non-clinical	0%	0%	0%
	Phase 1	0%	0%	0%
	Phase 2	0%	0%	0%
	Phase 3	0%	0%	5%
	FDA Review	0%	0%	7%
	Phase 4	0%	0%	NA
Biomarkers as Surrogate Endpoints	Non-clinical	0%	0%	0%
	Phase 1	0%	0%	4%
	Phase 2	-5%	-7%	7%

Element	Phase	Cost	Duration	Success Likelihood
	Phase 3	-15%	-14%	10%
	FDA Review	0%	0%	4%
	Phase 4	0%	0%	NA
Electronic Health Records	Non-clinical	0%	0%	0%
	Phase 1	0%	0%	0%
	Phase 2	-2%	-1%	0%
	Phase 3	-2%	-1%	6%
	FDA Review	0%	0%	6%
	Phase 4	0%	0%	NA
Patient Registries	Non-clinical	0%	0%	0%
	Phase 1	0%	0%	0%
	Phase 2	0%	0%	0%
	Phase 3	0%	0%	0%
	FDA Review	0%	0%	0%
	Phase 4	0%	0%	NA
Adaptive Design	Non-clinical	0%	0%	0%
	Phase 1	0%	-4%	0%
	Phase 2	-1%	-5%	0%
	Phase 3	-2%	-2%	0%
	FDA Review	0%	0%	0%
	Phase 4	0%	0%	NA
Standardized Contracts	Non-clinical	0%	0%	0%
	Phase 1	0%	-2%	0%
	Phase 2	0%	-2%	0%
	Phase 3	0%	-2%	0%
	FDA Review	0%	0%	0%
	Phase 4	0%	0%	NA
CDC/NIH Developing Epidemiological Data on Disease Incidence	Non-clinical	0%	0%	0%
	Phase 1	0%	0%	0%
	Phase 2	0%	0%	0%
	Phase 3	-1%	-1%	0%
	FDA Review	0%	0%	0%
	Phase 4	0%	0%	NA
Federally-supported cGMP-compliant Manufacturing Facilities	Non-clinical	0%	0%	0%
	Phase 1	-8%	0%	0%

Element	Phase	Cost	Duration	Success Likelihood
	Phase 2	-8%	0%	0%
	Phase 3	-8%	0%	0%
	FDA Review	0%	0%	0%
	Phase 4	-16%	0%	NA

NA = Not applicable

The zero percentages represent those cases where an expert indicated that the strategy was not relevant to a particular phase and/or cost, duration, or probability of phase transition success associated with that phase.

Table 11. Estimated Impacts of Clinical Trial Strategies on Baseline Cost, Duration, and Phase Transition Success Probability – Preventive Vaccines

Strategy	Change from Baseline due to…							
	Change in Cost		Change in Duration		Change in Success Probability		Total Change [a]	
	$	%	$	%	$	%	$	%
Wider Use of Mobile Technologies, Including Electronic Data Capture (EDC)	-$26.7	-2.6%	-$30.7	-2.9%	-$6.0	-0.6%	-$62.6	-6.0%
Simplified Clinical Trial Protocols and Reduced Amendments	-$28.4	-2.7%	-$40.5	-3.9%	$0.0	0.0%	-$68.3	-6.5%
Reduced Source Data Verification (SDV)	-$3.9	-0.4%	$0.0	0.0%	$0.0	0.0%	-$3.9	-0.4%
Improvements in FDA Review Process Efficiency	-$1.2	-0.1%	-$23.8	-2.3%	-$125.3	-12.0%	-$147.1	-14.1%
Staged Approval Process	$0.0	0.0%	$0.0	0.0%	-$110.2	-10.6%	-$110.2	-10.6%
Biomarkers as Surrogate Endpoints	-$38.0	-3.6%	-$62.2	-6.0%	-$195.6	-18.7%	-$276.8	-26.5%
Use of Electronic Health Records	-$6.3	-0.6%	-$6.4	-0.6%	-$110.3	-10.6%	-$121.6	-11.6%
Use Registry Data	NE	NE	NE	NE	NE	NE	NE	NE
Encourage Adaptive Design	-$5.7	-0.5%	-$25.3	-2.4%	-$6.0	-0.6%	-$36.8	-3.5%
Standardized Contracts	$0.0	0.0%	-$15.7	-1.5%	$0.0	0.0%	-$15.7	-1.5%
CDC/NIH Developing Epidemiological Data on Disease Incidence	-$5.0	-0.5%	-$4.3	-0.4%	$0.0	0.0%	-$9.3	-0.9%
Federally Supported cGMP-compliant Manufacturing Facilities	-$33.4	-3.2%	$0.0	0.0%	$0.0	0.0%	-$33.4	-3.2%

NE = Not estimated. Insufficient number of expert responses to estimate impacts.

[a] The sum of changes from baseline for individual elements do not sum to total change due to rounding and the fact that some impacts when examined jointly can have offsetting effects.

From Table 11, the strategy with the largest impact on overall development costs is Biomarkers as Surrogate Endpoints (-26.4 percent), followed by Improvements in FDA Review Process Efficiency and Interactions (-14.1 percent), Use of Electronic Health Records (11.7 percent), and implementation of a Staged Approval Process (10.6 percent). Those strategies with the lowest expected development cost savings include Reduced SDV (0.4 percent) and CDC/NIH Developing Epidemiological Data on Disease Incidence (0.9 percent).

7 DISCUSSION

This study uses a bottom-up approach to estimate PVac development costs. There are a handful of studies that have evaluated overall costs as well as those associated with different stages of vaccine development as depicted in Table 12. However, it is difficult to compare the estimates developed in this study with those in others as the R&D components captured across the different studies vary. Nonetheless, the total development cost (without post-approval costs) estimated in this study is within the range reported in Light et al. (2009), Wilson (2010), and that in World Health Organization (2016).

It is important to note that the estimated costs presented in this study do not include some significant elements, such as development of chemistry, manufacturing and controls (CMC) which could exceed $50 million (around $55 million in 2018 $) in cost in addition to over 80 person-years in human resources (Plotkin, et al., 2017), and manufacturing plant design and build, which could range from $50 million to $500 million ($62 million to $620 million in 2018 $) (Wilson, 2010; Plotkin, et al., 2017). One study estimated these manufacturing costs at $177-$696 million for RotaTeq, and at $165-$506 million for Rotarix (Light, et al., 2009).[7] Another category of costs that is missing from our estimates, are costs associated with establishing supply and distribution chains. The associated cost with this activity could be sizable because it requires extensive infrastructure, logistical and operational planning. Such costs can vary depending on the scale of distribution, target population(s) for the given PVac, and geographic reach. For example, Pfizer/BioNTech COVID-19 vaccine required significant investments in cold-chain logistics for ultra-cold storage and specialized packaging (Fahrni, et al., 2022).

[7] The corresponding values reported in Light et al. (2009) are $137-$539 and $128-$392 million in 2009 dollars, respectively.

Table 12. R & D Costs Reported in the Literature for Vaccines Compared to This Study (in Million $ 2018) [a]

Development Stage	Type of Cost	This Study	Wilson (2010)	Light et al. (2009)	World Health Organization (2016)	Chit et al. (2014) [b]	Gouglas et al. (2018) [c]
Non-clinical	Out of Pocket	$13.8	$6.2 to $18.5		$6.9 to $17.1	NA	$1.7 to $98.8
	Risk-adjusted	$144.9	NA		$76.0 to $599.2	$357.0	NA
Clinical Phases	Out of Pocket	$125.5	NA	$164.4 to $266.8	$130.5 to $154.4	NA	NA
	Risk-adjusted	$218.9	NA	NA	$295.0 to $428.4	$257.7	NA
Phase 1	Out of Pocket	$6.5	$4.9 to $12.3	$0.05 to $0.34	$2.3 to $2.6	$2.1	$1.9 to $53.4
	Risk-adjusted	$30.2	NA	NA	$11.3 to $38.7	NA	NA
Phase 2	Out of Pocket	$14.6	$4.9 to $12.3	$1.2 to $3.1	$13.6 to $14.3	$11.3	$3.9 to $93.6
	Risk-adjusted	$42.6	NA	NA	$54.5 to $114.7	NA	NA
Phase 3	Out of Pocket	$104.4	$61.7 to $148.2	$163.1 to $263.4	$114.6 to $137.5	$55.4	
	Risk-adjusted	$146.0	NA	NA	$229.2 to $275.0	NA	NA
FDA Review	Out of Pocket	$3.1	$2.5 to $3.7	NA	NA	NA	NA
	Risk-adjusted	$28.1	NA	NA	NA	NA	NA
Post-approval Study	Out of Pocket	$13.4	NA	NA	NA	NA	NA
	Risk-adjusted	$13.4	NA	NA	NA	NA	NA
Total (without post-approval study costs)	**Out of Pocket**	**$142.4**	**$74.1 to $179.0**	**$164.4 to $266.8**	**NA**	**NA**	**NA**
	Risk-adjusted	**$391.9**	**$166.7 to $432.2**	**$222.0 to $831.0**	**$371.0 to $1,027.5**	**$614.7**	**NA**
Total (with post-approval study costs)	**Out of Pocket**	**$155.8**	**NA**	**NA**	**NA**	**NA**	**NA**
	Risk-adjusted	**$405.2**	**NA**	**NA**	**NA**	**NA**	**NA**

NA = Not available

[a] All reported costs are converted to 2018 dollars for comparability using the Medical Care Index.

[b] The reported figures have been converted to US dollars from Canadian dollars. Additionally, the costs presented in the study are for a seasonal influenza vaccine.

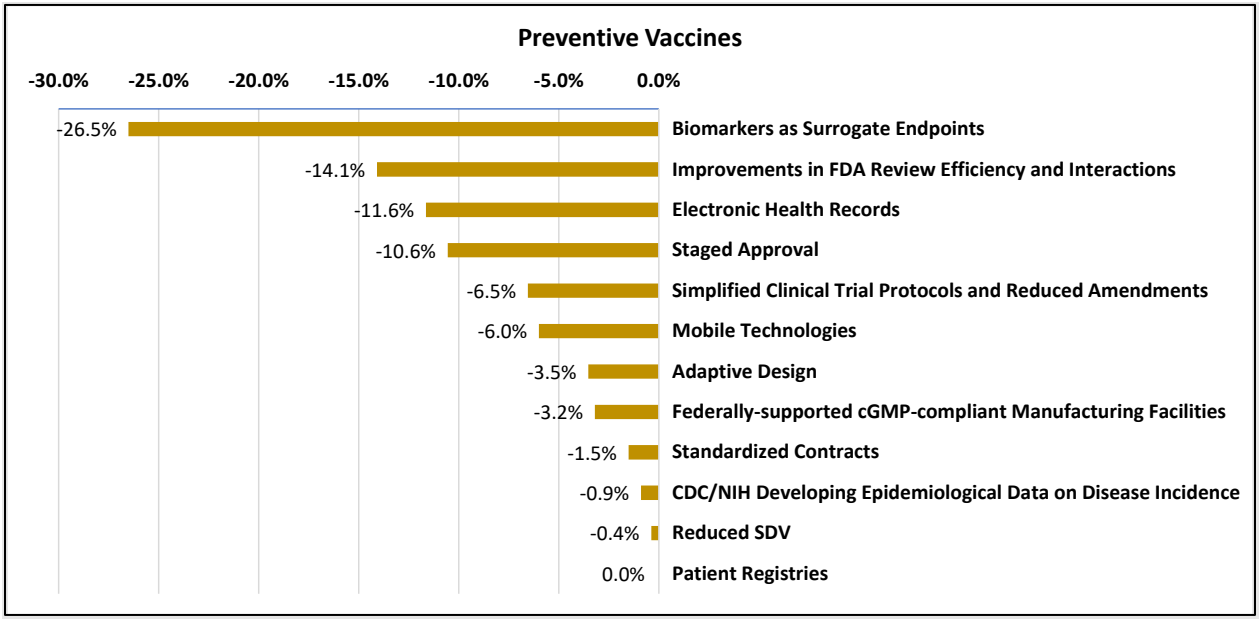
[c] The reported bounds are for those vaccines that are modeled in the high-cost and high-probability-of-success scenario.

8 CONCLUSIONS

Similar to other published studies (Chit, et al., 2014; Gouglas, et al., 2018; Light, et al., 2009; World Health Organization, 2016), we find that clinical trials comprise the largest portion of overall PVac development costs (Table 9). Clinical phase costs account for around 88 percent for PVacs. While our finding on the relative contribution of clinical trial costs to overall R&D expenditures is in line with other published studies, the estimated magnitude of these costs is different. Our estimate of average clinical phase cost ($105.5 million) is lower than those reported by Light et al. (2009) from $164.4 to $266.8 million and the World Health Organization (2016) from $130.5 to $154.4 million. When capital costs and the fact that not all products move successfully from one development stage to another are taken into account, the share of non-clinical stage costs rises from 10 percent to 58 percent for PVacs. Given the sizable contribution of non-clinical phase costs to overall expected capitalized costs, further research into this stage is needed.

Using the information from experts and other relevant data on product development costs, we estimate how implementation of the strategies impact PVac development costs (Figure 2). The strategy with the largest expected impact on overall development costs is biomarkers as surrogate endpoints (-26.5 percent), followed by improvements in FDA review process efficiency and interactions (-14.1 percent), use of electronic health records (-11.6 percent), and implementation of a staged approval process (-10.6 percent). Those strategies with the lowest expected development cost savings include reduced SDV (-0.4 percent) and CDC/NIH developing epidemiological data on disease incidence (-0.9 percent).

Figure 2. Estimated Impacts on Expected Capitalized Development Costs (Inclusive of Post-approval Costs) for Preventive Vaccines Across Strategies (in Percentages)



Notes: The zero percentages represent those cases where an expert indicated that the strategy was not relevant to a particular phase and/or cost, duration, or probability of phase transition success associated with that phase.

There are several limitations to this study. First, the impact estimates associated with the strategies identified represent the collective opinion of a small expert panel. As with any expert elicitation study, the opinions of experts are subject to known biases, such as availability, over/under-confidence, and representativeness. Second, the mental model each expert used in thinking about a strategy, i.e., what it encompasses and how it is implemented, is unknown but likely highly varied. The cognitive burden of the elicitation, which involved inquiring about hundreds of parameters (Eastern Research Group, Inc., 2022), required a trade-off between depth and breadth, precluding in-depth follow-up discussions with the expert participants. Third, as noted earlier, there have been significant developments in clinical research due to the COVID-19 pandemic that are not captured due to the timing of this study. Significant headway has been made in adopting several strategies highlighted in this study according to recent discussions with experts and federal staff. Finally, in evaluating impacts, our experts did not take into account the resource requirements and/or resulting externalities associated with a given strategy. For example, provision of more opportunities to identify, discuss, and resolve substantive issues to PVac developers during the BLA review process implies more FDA reviewer time spent on those applications which, in turn, requires additional resources (i.e., more FDA reviewers) than current levels. Adoption of a staged approval process might miss rare but severe adverse effects that only emerge in larger more diverse populations and/or population-specific efficacy resulting in suboptimal protection in certain groups. Even in the absence of such adverse findings, perception of a "rushed" approval by the public may erode trust in FDA.

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