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BRIEF
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New Estimates of the Cost of Preventive Vaccine Development and Potential Implications from the COVID-19 Pandemic

A reduced timeline for the clinical phase of vaccine development could be associated with a reduction of up to 50% in total vaccine development costs

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KEY POINTS

- Using public and proprietary sources, we estimate the research and development cost and duration associated with bringing novel vaccines to the U.S. market.
- Bringing a novel vaccine to the U.S. market costs an estimated $886.8 million on average, and its development process lasts 10 years.
- Technological innovation, large public investments, increased review resources, and greater interaction with industry were among some of the activities that occurred during the COVID-19 pandemic and that contributed to reducing the COVID-19 vaccine development process to around 2 years.
- Speeding the vaccine development timeline could be associated with up to 50% in reduced development costs.

BACKGROUND

Preventive vaccines have played a vital role in decreasing the incidence of infectious disease as well as resulting disability and mortality from infectious diseases. Preventive vaccines not only offer protection to those who receive them (including sometimes by making a disease course less severe), but they also contribute to community protection by decreasing disease transmission. The COVID-19 pandemic emphasized the role of preventive vaccines in public health. According to recently published estimates,[1,2,3,4] COVID-19 vaccination prevented millions of new cases and hospitalizations as well as hundreds of thousands of deaths in

[1] X. Chen, H. Huang, J. Ju, R. Sun and J. Zhang, "Impact of Vaccination on the COVID-19 Pandemic in U.S. States," *Scientific Reports,* vol. 12, no. 1, pp. 1554. doi: 10.1038/s41598-022-05498-z, 2022.

[2] M. Fusco, K. Marczell, K. Deger, M. Moran, T. Wiemken, A. Cane, S. de Boisvilliers, J. Yang, S. Vaghela and J. Roiz, "Public Health Impact of the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2) in the First Year of Rollout in the United States," *Journal of Medical Economics,* vol. 25, no. 1, pp. 605-617. doi: 10.1080/13696998.2022.2071427, 2022.

[3] S. Gupta, J. Cantor, K. Simon, A. Bento, C. Wing and C. Whaley, "Vaccinations Against COVID-19 May Have Averted Up To 140,000 Deaths In The United States," *Health Affairs (Millwood),* vol. 40, no. 9, pp. 1465-1472. doi: org/10.1377/hlthaff.2021.00619, 2021.

[4] N. Holtkamp, A. Kolbe and T. Beleche, " COVID-19 Vaccination Associated with Reductions in COVID-19 Mortality and Morbidity in the United States, and an Approach to Valuing these Benefits," US Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, Washington, DC, 2021.

the United States. It is estimated that these reductions in morbidity and mortality saved more than $30 billion in direct healthcare costs and $40 billion in indirect costs.[5]

The COVID-19 pandemic also produced changes that significantly sped up the COVID-19 vaccine development process. These included, among others, large US government investments in vaccine research and development (R&D) and use of other policies, such as the Defense Production Act that required companies to prioritize government contracts for medical supplies. There was also increased coordination across government and private partners domestically and abroad. U.S. government investment in COVID-19 vaccine development ranged from $10 billion[6] to $39.5 billion,[7,8] and the U.S. Food and Drug Administration (FDA) allocated substantial resources to developing COVID-19 vaccines and collaborated with private partners to prioritize clinical trials and gather real-world data.[9] FDA devoted significantly more review staff by deprioritizing work on other preventive vaccines to expedite reviews of COVID-19 vaccine applications.[10] These included issuing guidance for developers and launching initiatives to streamline regulatory review. FDA implemented process changes to reduce review times for COVID-19 vaccines and enable faster market launches. For example, FDA put in place additional management structures and maintained constant communication with COVID-19 vaccine developers to provide timely responses to questions. FDA also issued Emergency Use Authorizations (EUAs),[11] which allowed developers to bring their COVID-19 vaccines to market subject to EUA conditions when their Phase 3 trials reached a predetermined point sufficient to inform FDA's safety and efficacy review. EUAs were crucial for the initial batch of COVID-19 vaccines, allowing the temporary suspension of one vaccine while emergency safety concerns were addressed.[12] Companies were able to conduct certain clinical trial stages and manufacturing activities in parallel rather than sequentially,[13,14] shortening the development timeline to under 2 years.

This study used a transparent analytical model to better understand the scale and drivers of research and development (R&D) cost associated with bringing a new preventive vaccine to the U.S. market using a pre-COVID-19 vaccine development paradigm as a benchmark. It also examined the impact of pandemic-related policies on this benchmark cost estimate.

METHODS

Analytical Cost Model

Figure 1 presents a simplified diagram of the phases of preventive vaccine development, from conception through post-marketing.[15] Overall, preventive vaccine development has four distinct phases: pre-IND (development of rationale based on disease, immunogen identification, development of small-scale

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[5] Fusco et al., "Public Health Impact of the Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)" (see footnote 2).
[6] P. Ball, "The Lightning-fast Quest for COVID Vaccines — And What it Means for Other Diseases," *Nature,* vol. 589, pp. 16-18. doi: https://doi.org/10.1038/d41586-020-03626-1, 2021.
[7] R. Frank, L. Dach and N. Lurie, "It Was The Government That Produced COVID-19 Vaccine Success," *Health Affairs Blog,* vol. May 14, p. doi: 10.1377/hblog20210512.191448, 2021.
[8] H. Lalani, J. Avorn and A. Kesselheim, "US Taxpayers Heavily Funded the Discovery of COVID-19 Vaccines," *Clinical Pharmacology & Therapeutics,* vol. 111, no. 3, pp. 542-544. doi:10.1002/cpt.2344, 2021.
[9] A. Anand Shah, K. Kadakia, P. Marks, P. Cavazzoni and S. Hahn, "FDA Initiatives To Accelerate The Development Of COVID-19 Therapeutics," *Health Affairs Forefront,* p. doi: 10.1377/forefront.20200814.351515, 18 August 2020.
[10] P. M. (. C. a. D. C. (. CBER), Interviewee, *Personal communication.* [Interview]. 3 February 2023.
[11] U.S. Food and Drug Administration, "Emergency Use Authorization for Vaccines Explained," 20 November 2020. [Online]. Available: https://www.fda.gov/vaccines-blood-biologics/vaccines/emergency-use-authorization-vaccines-explained. [Accessed 21 August 2023].
[12] A. Tran and T. Witek, "The Emergency Use Authorization of Pharmaceuticals: History and Utility During the COVID-19 Pandemic," *Pharmaceutical Medicine,* vol. 35, no. 4, pp. 203-213. doi: 10.1007/s40290-021-00397-6, 2021.
[13] M. Slaoui and M. Hepburn, "Developing Safe and Effective Covid Vaccines - Operation Warp Speed's Strategy and Approach," *New England Journal of Medicine,* vol. 383, no. 18, pp. 1701-1703. doi: 10.1056/NEJMp2027405, 2020.
[14] Ball, "The Lightning-fast Quest for COVID Vaccines" (see footnote 6).
[15] S. A. Plotkin, P. A. Offit, W. A. Orenstein and K. M. Edwards, Plotkin's Vaccines, 7th ed., Philadelphia: Elsevier, 2018.

manufacturing process, and nonclinical studies), pre-marketing/pre-licensure (FDA IND submission, scale-up and validation of manufacturing process, and clinical phases 1 through 3), licensing (submission of a biologics license application [BLA]), and post-marketing (ongoing large-scale manufacturing and post-marketing—Phase 4—studies).[16,17,18]

To develop the analytical model of preventive vaccine development, we selected 14 out of the 82 preventive vaccines licensed for use in the United States from November 2019 through January 2000 as a sample (Table 1). These vaccines were categorized as novel by Plotkin et al. [19] For each, we identified clinical trials conducted to support the BLA and information on pre-IND activities.[20,21,22,23]

Table 1. Study Preventive 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

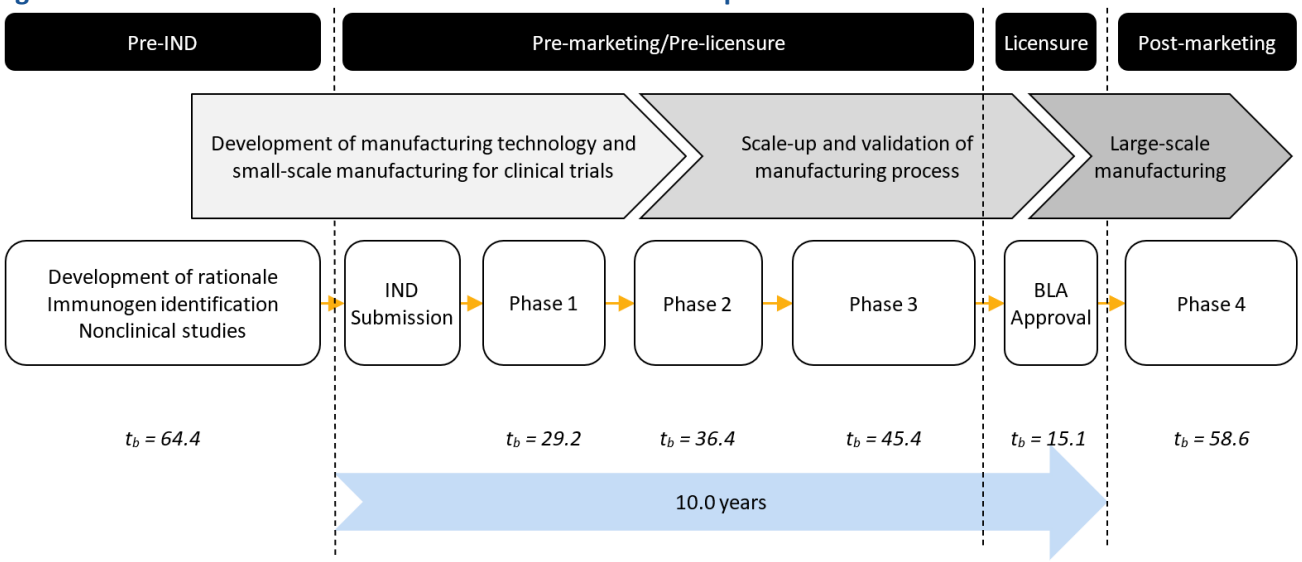
Vaccine sample selection criteria: whether a vaccine was approved on or after 2000, novel, deemed important by Plotkin et al.,[24] and whether it had publicly available FDA BLA submission information. Source: FDA.[25]

[16] *Ibid.*
[17] N. Lurie, M. Saville, R. Hatchett and J. Halton, "Developing Covid-19 Vaccines at Pandemic Speed," *The New England Journal of Medicine,* vol. 382, pp. 1969-1973. doi: 10.1056/NEJMp2005630, 2020.
[18] A. Sertkaya, C. Berger, "Preventive Vaccine Development—Final Report," Eastern Research Group, Inc., Concord, MA, 2022.
[19] Plotkin et al., Plotkin's Vaccines (see footnote 15).
[20] U.S. Food and Drug Administration, "Vaccines Licensed for Use in the United States," 2019a. [Online]. Available: https://www.fda.gov/vaccines-blood-biologics/vaccines/vaccines-licensed-use-united-states. [Accessed 8 November 2019].
[21] U.S. Food and Drug Administration, "Advisory Committee Calendar," 2021e. [Online]. Available: https://www.fda.gov/advisory-committees/advisory-committee-calendar. [Accessed 9 September 2021].
[22] U.S. Food and Drug Administration, "Advisory Committee Calendar," 2017. [Online]. Available: http://wayback.archive-it.org/7993/20170110233952/http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm. [Accessed 9 September 2021].
[23] U.S. Food and Drug Administration, "Meeting Materials, Vaccines and Related Biological Products Advisory Committee," 2021f. [Online]. Available: https://www.fda.gov/advisory-committees/vaccines-and-related-biological-products-advisory-committee/meeting-materials-vaccines-and-related-biological-products-advisory-committee. [Accessed 9 September 2021].
[24] Plotkin et al., Plotkin's Vaccines (see footnote 15).
[25] U.S. Food and Drug Administration, "Vaccines Licensed for Use in the United States" (see footnote 19).

Analytical Cost Model Parameters

For each phase of development (Figure 1), we estimated six parameters: phase duration, total elapsed time between the start of one development phase and the start of the next (start-to-start), number of patients enrolled, per-patient cost, transition success probability, and cost of capital (Table 2).[26] We estimated 11% as the cost of capital based on estimated value for the biopharmaceutical sector.[27,28]

Figure 1. Overview of Traditional Preventive Vaccine Development



Source: Adapted from Plotkin, et al. (2018) and Lurie, et al. (2020)

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

Parameter	Phase	Value	Source
Phase durations (months)	Nonclinical	64.4	Published studies; study 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 (months)	Nonclinical to phase 1	64.4	Published studies
	Phase 1 to Phase 2	14.6	Study 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; study vaccine sample
Average number of patients	Nonclinical	NA	
	Phase 1	149	Study vaccine sample
	Phase 2	3,911	
	Phase 3	23,179	
	FDA BLA review	NA	
	Phase 4	12,794	Study vaccine sample
	Nonclinical	NA	Not applicable
	Phase 1	$38,130	Published studies; study vaccine sample

[26] Sertkaya and Berger, "Preventive Vaccine Development—Final Report" (see footnote 18).

[27] *Ibid.*

[28] S. Harrington, "Cost of Capital for Pharmaceutical, Biotechnology, and Medical Device Firms," in *The Oxford Handbook of the Economics of the Biopharmaceutical Industry*, P. Danzon and S. Nicholson, Eds., New York, Oxford University Press, 2012, pp. 75-99.

Parameter	Phase	Value	Source
Average per-patient costs ($, 2018)	Phase 2	$3,268	
	Phase 3	$3,753	
	FDA BLA review	NA	Not applicable
	Phase 4	$1,044	Calculated as the ratio of total out-of-pocket costs reported in published studies to average number of patients
Out of Pocket Phase Costs ($, 2018)	Non-clinical	$11,841,009	Published studies
	Phase 1	$5,673,733	Calculated as the product of average cost per patient and average number patients enrolled for the phase
	Phase 2	$12,782,945	
	Phase 3	$86,994,393	
	FDA BLA review	$2,057,912	Published studies
	Phase 4	$13,362,423	Calculated as the product of average cost per Phase 4 clinical trial study and average number of clinical trials conducted for Phase 4
Transition success probabilities (%)	Nonclinical 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

Estimating Preventive Vaccine Development Cost

Benchmark Scenario

We developed an analytical cost model to estimate three measures of the cost of preventive vaccine development.[29] The first measure represents the average cash outlay paid by the developer for a single preventive vaccine from the nonclinical stage through post-marketing. The second measure is the mean expected cost, which includes the cost for successful preventive vaccines as well as expenditures on those preventive vaccines that fail. To incorporate probabilities of failure at each stage of the process, we calculated the expected cost of each preventive vaccine development stage by dividing the cost estimated for that stage by the aggregate phase-specific probability of the product successfully making it to market.

The third measure, the mean expected capitalized cost, accounts for the cost, duration, probability of successfully transitioning from one development stage to the next, and the cost of capital. For each stage of the development process, we used the estimated mean expected cost over the duration of that stage[30] and a cost of capital rate of 11%. We then calculated the mean expected capitalized cost of the Phase 2 study stage, which we estimated to last 34.2 months, at $95.5 million. Finally, we calculated the mean expected capitalized cost of preventive vaccine development by summing the estimated mean expected capitalized cost for each development stage.

Next, we estimated the same three measures of development costs for each of the 14 preventive vaccines in our sample by using the preventive vaccine-specific data collected on start-to-start durations and clinical trial parameters from the publicly available information sources.[31] The remaining model parameters did not vary across the 14 preventive vaccines and were assumed identical to those presented in Table 2. All estimates were derived from data collected before 2020, which reflected the benchmark scenario (see top panel of Figure 2).

[29] J. DiMasi, H. Grabowski and R. Hansen, "Innovation in the Pharmaceutical Industry: New Estimates of R&D Costs," *Journal of Health Economics,* vol. 47, pp. 20-33, 2016.
[30] *Ibid.*
[31] Sertkaya and Berger, "Preventive Vaccine Development—Final Report" (see footnote 18).

Pandemic Scenario

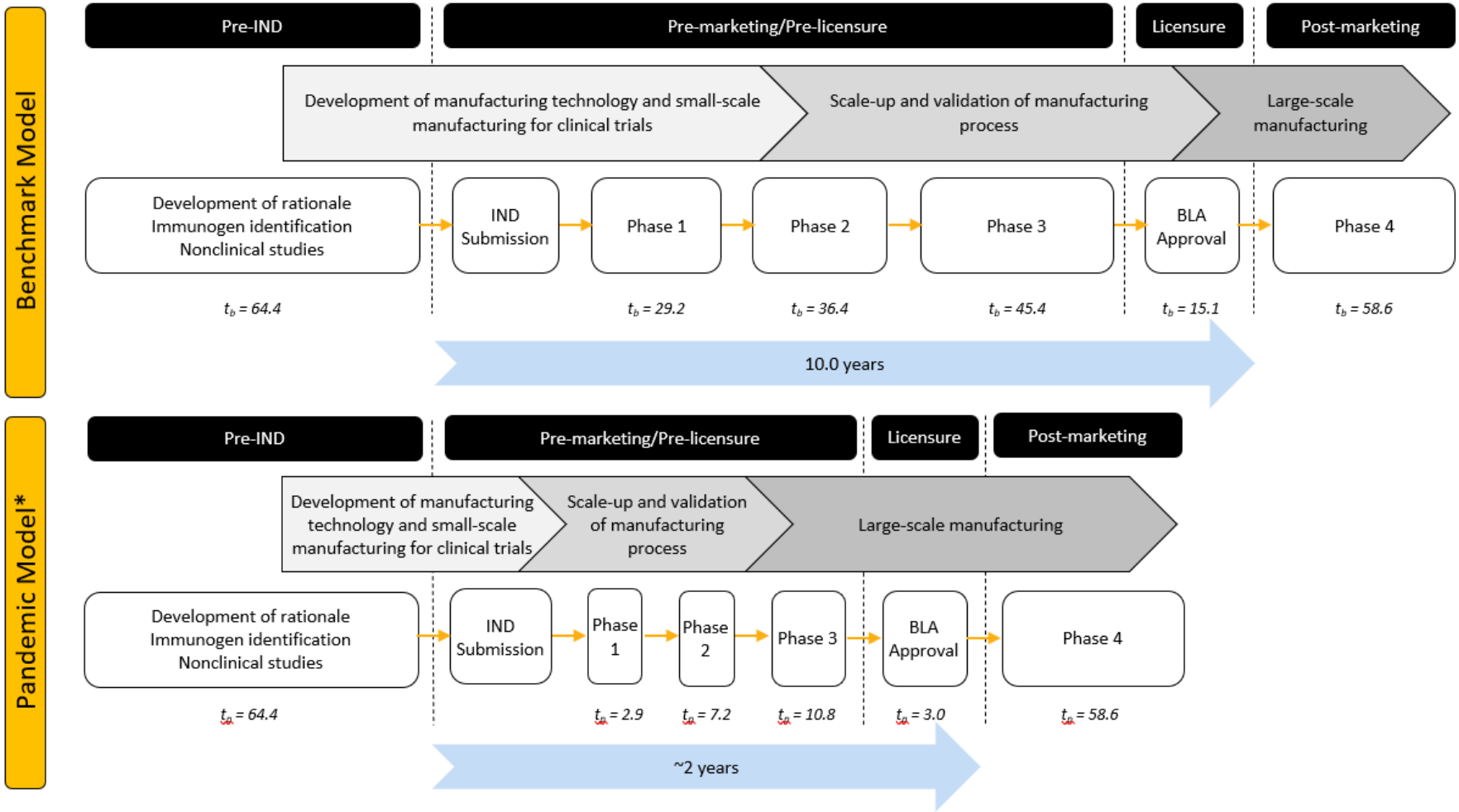
Under this scenario (the bottom panel of Figure 2), we estimated the cost of bringing a preventive vaccine to market using the phase-specific development duration data from two COVID-19 vaccines and making simplifying assumptions about the other model parameters. We then adjusted the start-to-start model parameters proportionally such that the sum of Phase 1 to Phase 2, Phase 2 to Phase 3, Phase 3 to BLA submission, and BLA submission to approval equaled 24 months. We did not make any adjustments to the other model parameters. Based on the clinical trial data from the two COVID-19 mRNA vaccines, the average number of patients by phase was about the same as the average number of patients in the baseline scenario. Taken together, our assumptions imply that it did not take additional resources to do the required work in less time. Specifically, we assume that costs associated with key clinical trial conduct and review activities such as patient retention and recruitment, site and administrative staff management, data collection, clinical procedures, were unchanged relative to the baseline scenario. However, shortages of medical supplies and the healthcare workforce indicate that some costs might have increased during the pandemic.[32,33] It is also possible that adoption of certain technologies could translate into reduced costs.[34]

[32] U.S. Department of Health and Human Services, "Impact of the COVID-19 Pandemic on the Hospital and Outpatient Clinician Workforce," U.S. HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE), Washington, DC, 2022.

[33] Eastern Research Group, Inc., "Examination of Clinical Trial Costs and Barriers for Drug Development," U.S. HHS Office of the Assistant Secretary for Planning and Evaluation (ASPE), Washington, DC, 2014.

[34] F. Collins, S. Adam, C. Colvis, E. Desrosiers, R. Draghia-Akli, A. Fauci, M. Freire, G. Gibbons, M. Hall, E. Hughes, K. Jansen, M. Kurilla, H. Lane, D. Lowy, P. Marks, J. Menetski, W. Pao, E. Pérez-Stable, L. Purcell, S. Read, J. Rutter and M. Santos, "The NIH-led Research Response to COVID-19," *Science,* vol. 379, pp. 441-444. doi:10.1126/science.adf5167, 2023.

Figure 2. Comparison of Benchmark Preventive Vaccine Development Model to Pandemic Model*



Source: Adapted from Plotkin, et al. (2017) and Lurie, et al. (2020).[16]
t_b = Duration for the development stage in months under benchmark model
t_p = Duration for the development stage in months under pandemic model

***The pandemic model involved the issuance of a Public Health Emergency (issued under section 319 of the Public Health Service Act) and a declaration that an emergency use authorization was appropriate (issued under section 564 of the Federal Food, Drug and Cosmetic Act) before issuance of the IND. It also included some preventive vaccine candidates for which pre-clinical activity had been ongoing prior to the Public Health Emergency.**

FINDINGS

Benchmark Scenario Estimates

We estimated the mean development cost for a preventive vaccine at $132.7 million (95% CI: $84.3million-$199.5 million), including Phase 4 studies (Table 3) but excluding other significant costs, such as development of chemistry, manufacturing and controls (CMC), manufacturing plant design and build as well as costs associated with establishing supply and distribution chains. Of these costs, 8.9% were nonclinical-stage related, 79.5% were clinical stage-related, 1.6% were for the FDA BLA review stage, and the remaining 10.1% were associated with Phase 4. The expected capitalized mean development cost, including Phase 4, was $886.8 million (95% CI: $387.3 million-$4,502.1 million). On average, the estimated time to regulatory approval and subsequent market launch was 15.3 years (95% CI: 7.3-28.1 years) from the start of nonclinical stage and 10.0 years (95% CI: 5.1-17.1 years) from the beginning of clinical phase.

Table 3. Mean Cost of Developing a Preventive Vaccine for the U.S. Market (Million $ 2018)

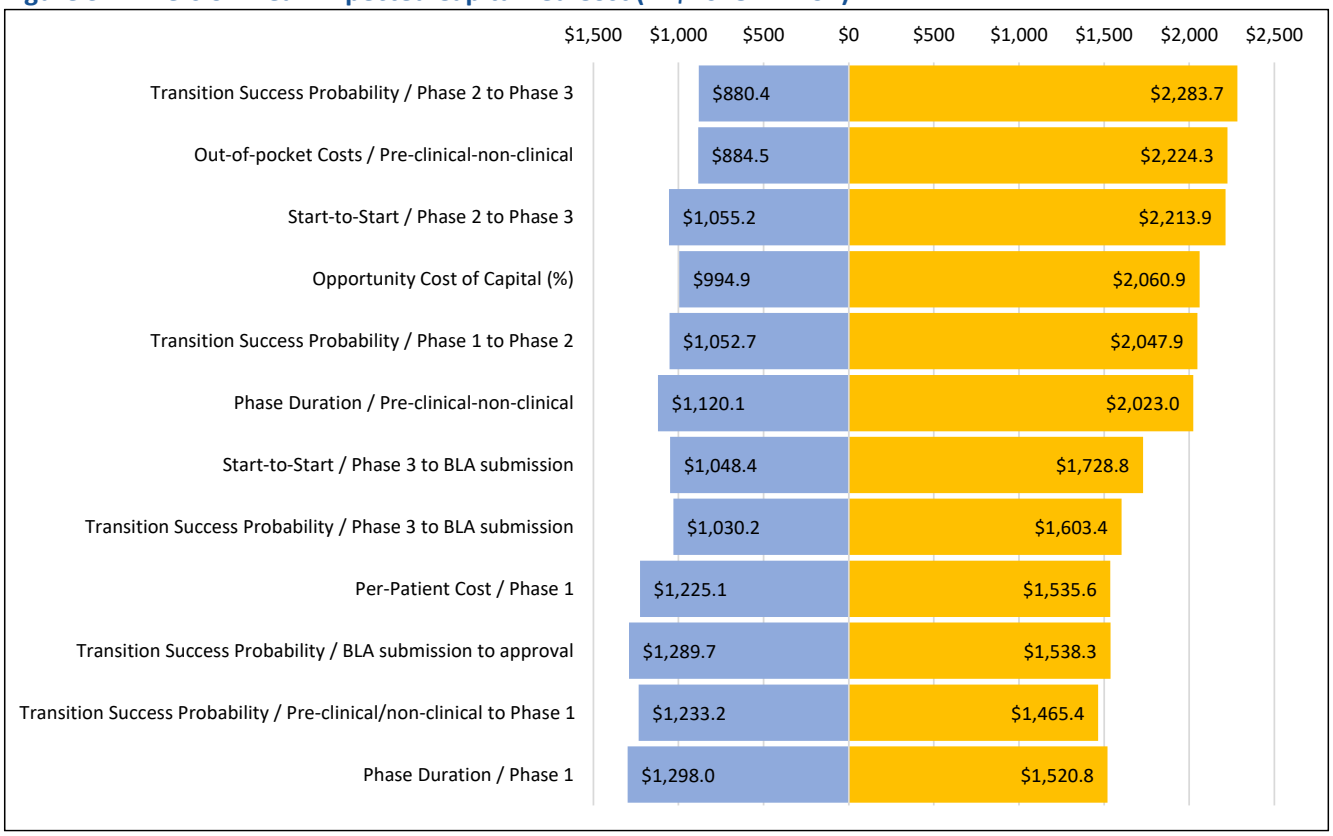
Development Stage	Approval probability [a]	Mean out-of-pocket costs (in $ 2018) [b]		Mean expected out-of-pocket costs (in $, 2018) [c]		Mean expected capitalized out-of-pocket costs (in $, 2018) [d]	
		$	%	$	%	$	%
Nonclinical phase	9.4%	$11.8	8.9%	$126.2	36.5%	$512.6	57.8%
Clinical phases	NA	$105.5	79.5%	$187.6	54.2%	$343.7	38.8%
Phase 1 [e]	21.1%	$5.7	4.3%	$26.8	7.8%	$70.2	7.9%
Phase 2 [e]	32.7%	$12.8	9.6%	$39.1	11.3%	$86.7	9.8%
Phase 3 [e]	71.5%	$87.0	65.6%	$121.7	35.2%	$186.9	21.1%
FDA BLA review	94.2%	$2.1	1.6%	$18.7	5.4%	$20.1	2.3%
Phase 4	NA	$13.4	10.1%	$13.4	3.9%	$10.3	1.2%
Total without Phase 4 costs	**NA**	**$119.3**	**89.9%**	**$332.6**	**96.1%**	**$876.4**	**98.8%**
Total with Phase 4 costs	**NA**	**$132.7**	**100.0%**	**$346.0**	**100.0%**	**$886.8**	**100.0%**

NA = Not available
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] Expected capitalized costs take into account the costs of failures and the time value of money.
[e] The out-of-pocket cost is estimated as the product of average cost per patient and the total number of patients for that phase.

From an expected capitalized cost perspective, the share of cost represented by the nonclinical stage was 57.8% and 2.3%. The nonclinical stage represents the largest portion of total expected capitalized development cost, primarily because the probability of moving from the nonclinical stage to a marketable preventive vaccine is only 9.4%. The odds of a preventive vaccine making it to market is higher if it has already cleared Phase 1. The mean development cost estimates varied across the 14 vaccines in the sample (Appendix Figure 1).

The top five drivers of the mean expected capitalized cost, in order of importance, were: Phase 2 to Phase 3 transition success probability, nonclinical phase cost, Phase 2 to Phase 3 start-to-start duration, cost of capital, and Phase 1 to Phase 2 transition success probability (Figure 3). The relative rankings of these main cost drivers varied across our sample.

Figure 3. Drivers of Mean Expected Capitalized Cost (in $2018 Million)



Note: The bars of the tornado chart show how sensitive the estimated mean expected capitalized cost is to each model parameter as they change over their allowed ranges. The model parameters are ordered from most to least impact.

Pandemic Scenario Estimates

Our estimates suggest that the accelerated development timeline alone could be associated with up to a 50% reduction in total expected capitalized costs from $886.8 million to $454.4 million per vaccine (Figure 2). The reduction in the estimated costs is primarily due to the cost of capital because the development costs incurred are carried over (or "capitalized") for a shorter period compared to the baseline scenario. While our model cannot discern development cost offsets by funding source, the cost for developing these vaccines was largely borne by the U.S. government. For example, the U.S. government made significant investments in raw materials, consumables, needles/syringes, vials to ensure that these vaccines could be produced at large scale. Additionally, the U.S. government also covered the costs of establishing supply and distribution chains to ensure that these vaccines were available to all within a 5-mile radius. Our model also does not account for the costs associated with coordination and prioritization of COVID-19 pandemic-related activities by the U.S. government. Our analysis also assumes that large quantities of GMP-grade vaccine are manufactured much earlier in the development timeline because the financial risk was borne by the U.S. government, which companies may be unwilling to do at-risk for routine vaccines.

LIMITATIONS

Estimated costs do not include development of Chemistry, Manufacturing, and Controls (CMCs), which could exceed $55 million in addition to over 80 person-years in human resources,[35] and manufacturing plant design

[35] S. Plotkin, J. M. Robinson, G. Cunningham, R. Iqbal and S. Larsen, "The complexity and cost of vaccine manufacturing – An overview," *Vaccine,* vol. 35, no. 33, pp. 4064–4071, 2017. doi: 10.1016/j.vaccine.2017.06.003, 2017.

and build, which could range from $62 million to $620 million.[36,37] Another category of costs that is missing from our estimates, are costs for establishing supply and distribution chains. The associated cost of this activity could be sizable because it requires extensive infrastructure, logistical and operational planning. The pandemic estimate assumes that there were no changes in costs associated with workforce, site and participant costs, or other administrative costs. Key model parameters, such as phase transition success probabilities and phase durations, could vary based on vaccine type, innovation level, and disease target.[3835] Sectoral affiliation, track record of the sponsor, and platform technology all affect development costs.[39] Additionally, our sample selection criterion of "novel" was based on a classification at the time of approval and may not include recent technological advancements or designs to consider them novel now. If a later version of a given vaccine relied on clinical and/or other data generated for the prior version (obviating the need to conduct some or all clinical trials), this likely led to an underestimation of average vaccine development costs. Future studies could refine this analysis by 1) increasing the number of vaccines sampled, and 2) updating the definition of novel. While the total cost of development of the COVID-19 vaccines was largely borne by the U.S. government, our model cannot discern development cost offsets by funding source (private vs government).

DISCUSSION AND CONCLUSIONS

This study used a bottom-up analytical approach to estimate preventive vaccine development costs and duration. Across published studies (Appendix Table 1) that drew on development data from vaccines that targeted a wide range of pathogens such as those severe outbreak pathogens prioritized by the World Health Organization (WHO) or seasonal influenza,[40,41,42] Phase 3 is the costliest development phase, with cash outlays ranging from $60 million to over $148 million. Phase 1 is the least-costly stage, at an average of $6.5 million, while the average nonclinical phase ($13.8 million), Phase 2 ($14.6 million), and Phase 4 ($13.4 million) costs are comparable.

Clinical trials comprise the largest portion (89.6% including Phase 4 trials) of overall preventive vaccine development cost (Table 3). Average clinical phase cost ($105.5 million) is lower than those reported by Light et al.[43] from $164.4 to $266.8 million and the WHO[44] from $130.5 to $154.4 million. The difference in results may be due to differences in methodology and scope. 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. When capital costs and the fact that not all vaccine candidates move successfully from one development stage to another are considered, the share of nonclinical stage costs rises from 10% to 58%. Given the sizable contribution of nonclinical phase costs to overall expected capitalized costs, further research into this stage is needed.

The 14 vaccines in our sample are based on classical vaccine platforms, which are more costly to develop and require complex and time-consuming processes to manufacture. In contrast, next-generation vaccine

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[36] *Ibid.*

[37] P. Wilson, "Giving Developing Countries the Best Shot: An Overview of Vaccine Access and R&D," Campaign for Access to Essential Medicines, Geneva, Switzerland, 2010.

[38] Plotkin et al., "The complexity and cost of vaccine manufacturing – An overview" (see footnote 34).

[39] D. Gouglas, T. T. Le, K. Henderson, A. Kaloudis, T. Danielsen, N. C. Hammersland, J. M. Robinson, P. M. Heaton and J.-A. Rottingen, "Estimating the cost of vaccine development against epidemic infectious diseases: A cost minimization study," *The Lancet,* vol. 6, pp. e1386-e1396, 2018.

[40] World Health Organization, "An R&D Blueprint for Action to Prevent Epidemics - Funding and Coordination Models for Preparedness and Response," World Health Organization, Geneva, Switzerland, 2016.

[41] A. Chit, J. Parker, S. Halperin, M. Papadimitropoulosa, M. Krahna and P. Grootendorst, "Toward More Specific and Transparent Research and Development Costs: The Case of Seasonal Influenza Vaccines," *Vaccine,* vol. 32, p. 3336–3340, 2014.

[42] D. Gouglas et al, "Estimating the cost of vaccine development" (see footnote 38).

[43] D. Light, J. Andrus and R. Warburton, "Estimated Research and Development Costs of Rotavirus Vaccines," *Vaccine,* vol. 27, no. 47, pp. 6627-6633. doi: 10.1016/j.vaccine.2009.07.077, 2009.

[44] World Health Organization, "An R&D Blueprint for Action to Prevent Epidemics" (see footnote 39).

platforms have low-cost flexibility and can be rapidly and widely distributed.[45] The use of next-generation platforms during the COVID-19 pandemic enabled the rapid development of vaccine candidates, allowing for adjustments as viruses evolved and efficient scaling-up of production. Next-generation platforms offer potential for vaccine development for infectious diseases, as they could help reduce costs, improve production output, and speed up development.[46] However, challenges to developing next-generation vaccines call for continued research.[47] Additionally, it is not possible to estimate the impact of technological, financial, and regulatory factors on the reduction in development timelines from around 10 to 2 years during the COVID-19 pandemic. Next-generation vaccine platforms likely sped up development, as did increased coordination between FDA and industry. Moreover, the nature of the disease and clinical trial endpoints allowed for a very short follow-up period further accelerating the development timeline.

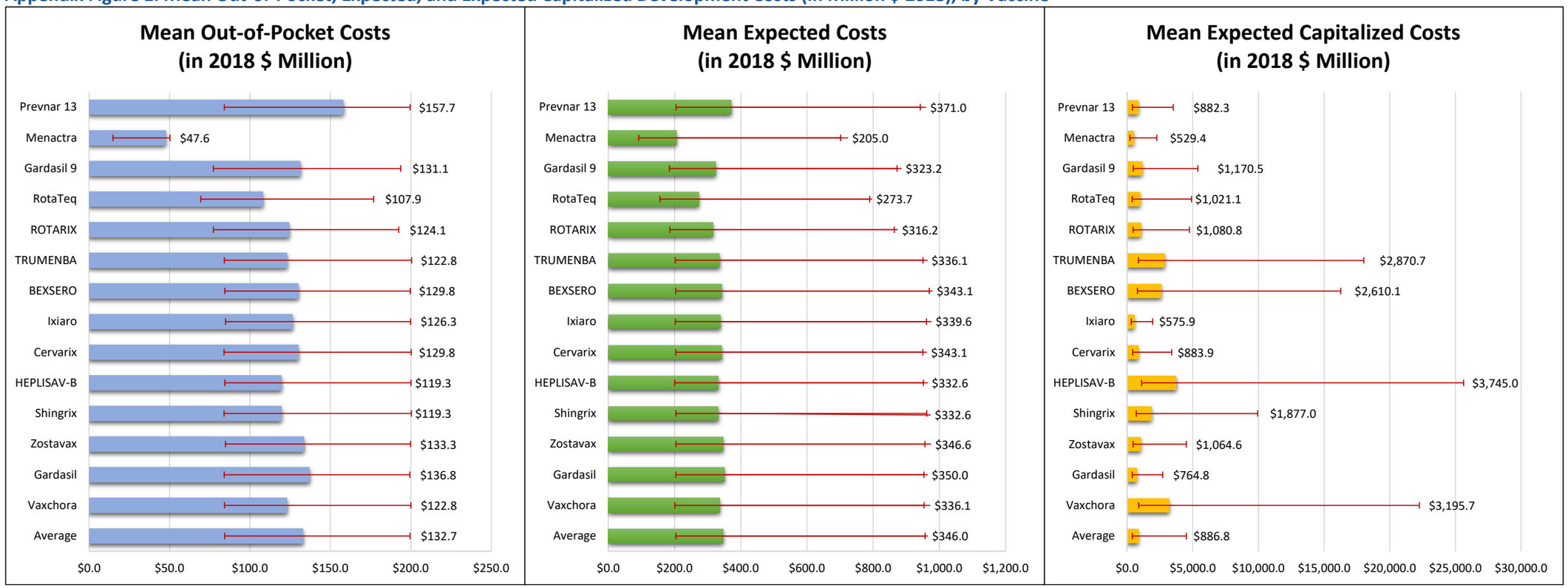
The COVID-19 pandemic demonstrated ways to improve the vaccine development process and reduce overall R&D costs, which included technological innovation (e.g., use of next generation vaccine development platforms), adoption of more streamlined internal processes and decision making by developers, the de-risking of the development process by sizeable public investment, and substantial FDA resources allocated to prioritizing COVID-19 vaccine development and review. During the pandemic, FDA went to great lengths to address the situation, such as enhancing the frequency and depth of their interactions with COVID-19 vaccine developers and providing remarkably fast feedback to them. In addition, the public investment allowed other agencies such as the Administration for Strategic Preparedness and Response (ASPR) to coordinate and support development of COVID-19 vaccines and treatments and increase manufacturing capacity. As a result, COVID-19 vaccines were brought to market at lightning speed and at less than half the typical cost of development. Future research could examine the lessons learned from the COVID-19 vaccine development program and applications to improve vaccine development timelines and reduce costs.

[45] M. Ghattas, G. Dwivedi, M. Lavertu and M. Alameh, "Vaccine Technologies and Platforms for Infectious Diseases: Current Progress, Challenges, and Opportunities," *Vaccines (Basel),* vol. 9, no. 12, p. 1490. doi: 10.3390/vaccines9121490, 2021.

[46] D. Morens, J. Taubenberger and A. Fauci, "Rethinking Next-generation Vaccines for Coronaviruses, Influenzaviruses, and Other Respiratory Viruses," *Cell Host Microbe,* vol. 31, no. 1, pp. 146-157. doi: 10.1016/j.chom.2022.11.016, 2023.

[47] Ghattas et al., "Vaccine Technologies and Platforms for Infectious Diseases" (see footnote 44).

Appendix Figure 1. Mean Out-of-Pocket, Expected, and Expected Capitalized Development Costs (in Million $ 2018), by Vaccine



Appendix Table 1. 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[37]	Light et al.[43]	WHO[40]	Chit et al.[41] [b]	Gouglas et al.[42] [c]
Nonclinical	Out of pocket	$13.8	$6.2–$18.5		$6.9–$17.1	NA	$1.7–$98.8
	Risk-adjusted	$144.9	NA		$76.0–$599.2	$357.0	NA
Clinical phases	Out of pocket	$125.5	NA	$164.4–$266.8	$130.5–$154.4	NA	NA
	Risk-adjusted	$218.9	NA	NA	$295.0–$428.4	$257.7	NA
Phase 1	Out of pocket	$6.5	$4.9–$12.3	$0.05–$0.34	$2.3–$2.6	$2.1	$1.9–$53.4
	Risk-adjusted	$30.2	NA	NA	$11.3–$38.7	NA	NA
Phase 2	Out of pocket	$14.6	$4.9–$12.3	$1.2–$3.1	$13.6–$14.3	$11.3	$3.9–$93.6
	Risk-adjusted	$42.6	NA	NA	$54.5–$114.7	NA	NA
Phase 3	Out of pocket	$104.4	$61.7–$148.2	$163.1–$263.4	$114.6–$137.5	$55.4	
	Risk-adjusted	$146.0	NA	NA	$229.2–$275.0	NA	NA
FDA review	Out of pocket	$3.1	$2.5–$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–$179.0**	**$164.4–$266.8**	**NA**	**NA**	**NA**
	Risk-adjusted	**$391.9**	**$166.7–$432.2**	**$222.0–$831.0**	**$371.0–$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 U.S. dollars from Canadian dollars. 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.

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