Pipeline analysis of a vaccine candidate portfolio for diseases of poverty using the Portfolio-To-Impact modelling tool [version 1; peer review: awaiting peer review]

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Abstract

Background: The Portfolio-To-Impact (P2I) P2I model is a recently developed product portfolio tool that enables users to estimate the funding needs to move a portfolio of candidate health products, such as vaccines and drugs, along the product development path from late stage preclinical to phase III clinical trials, as well as potential product launches over time. In this study we describe the use of this tool for analysing the vaccine portfolio of the European Vaccine Initiative (EVI). This portfolio includes vaccine candidates for various diseases of poverty and emerging infectious diseases at different stages of development.

Methods: Portfolio analyses were conducted using the existing assumptions integrated in the P2I tool, as well as modified assumptions for costs, cycle times, and probabilities of success based on EVI’s own internal data related to vaccine development.

Results: According to the P2I tool, the total estimated cost to move the 18 candidates currently in the EVI portfolio along the pipeline to launch would be about US $470 million, and there would be 0.69 cumulative expected launches during the period 2019-2031. Running of the model using EVI-internal parameters resulted in a significant increase in the expected product launches.

Conclusions: The P2I tool's underlying assumptions could not be tested in our study due to lack of data available. Nevertheless, we expect that the accelerated clinical testing of vaccines (and drugs) based on the use of controlled human infection models that are increasingly available, as well as the accelerated approval by regulatory authorities that exists for example for serious conditions, will speed up product development and result in significant cost reduction. Project findings as well as potential future modifications of the P2I tool are discussed with the aim to improve the underlying methodology of the P2I model.

Keywords

European Vaccine Initiative, vaccines, diseases of poverty, emerging infectious diseases, portfolio, P2I
This article is included in the TDR gateway.

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**Author roles:** Gunn A: Formal Analysis, Investigation, Methodology, Software, Writing – Original Draft Preparation; Bandara S: Formal Analysis, Investigation, Methodology, Software, Writing – Original Draft Preparation; Yamey G: Conceptualization, Funding Acquisition, Methodology, Writing – Original Draft Preparation; D'Alessio F: Investigation; Depraetere H: Investigation; Houard S: Investigation; Viebig N: Investigation; Jungbluth S: Conceptualization, Funding Acquisition, Project Administration, Supervision, Writing – Original Draft Preparation

**Competing interests:** No competing interests were disclosed.

**Grant information:** This work, Project ID Nº B80106, received financial support from TDR, the Special Programme for Research and Training in Tropical Diseases, co-sponsored by UNICEF, UNDP, the World Bank and WHO. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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**How to cite this article:** Gunn A, Bandara S, Yamey G et al. Pipeline analysis of a vaccine candidate portfolio for diseases of poverty using the Portfolio-To-Impact modelling tool [version 1; peer review: awaiting peer review] F1000Research 2019, 8:1066 (https://doi.org/10.12688/f1000research.19810.1)

**First published:** 11 Jul 2019, 8:1066 (https://doi.org/10.12688/f1000research.19810.1)
Introduction

The Special Programme for Research and Training in Tropical Diseases (TDR) recently developed a new modelling tool, called Portfolio-to-Impact (P2I), that allows users to model the impact of different research portfolios. The P2I tool can be used to estimate the costs of moving a portfolio of candidate products for poverty-related and neglected diseases (PRNDs) through the pipeline and the likely launches that would result. It can also help to identify potential funding bottlenecks and operational challenges. The modelling tool, which is deterministic, uses Excel based software to estimate the “minimum funding needs to accelerate health product development from late stage preclinical study to phase III clinical trials” and to “visualize potential product launches over time.”

To the best of our knowledge, the first published use of the tool was by Young and colleagues. These researchers first conducted a pipeline portfolio review to identify current candidates in the pipeline for 35 PRNDs. They then used the P2I tool to estimate (a) the costs to move these candidates through the pipeline, (b) the likely launches, and (c) the highly needed products that would still be “missing” at the end. As of August 31, 2017, they found 685 PRND product candidates, of which 538 candidates met inclusion criteria for input into the model. Their modelling estimated that it would cost about US$ 16.3 billion (range $13.4–19.8B) to move these candidates along the pipeline, resulting in about 128 (89–160) expected product launches. The study found that “there would be few launches of complex new chemical entities; launches of highly efficacious HIV, tuberculosis, or malaria vaccines would be unlikely.”

The European Vaccine Initiative (EVI), established in 1998 as the European Malaria Vaccine Initiative (EMVI), is a not-for-profit organization that supports the development of effective, affordable and accessible vaccines against diseases of poverty and emerging infectious diseases. To achieve this goal, EVI supports translational vaccine research and development (R&D) spanning from preclinical development through to the establishment of a clinical proof of concept. To date, EVI has supported the development of about 40 vaccine candidates through to early- and mid-stages of clinical development. Initially focussing only on malaria vaccines, in 2009 in the context of a strategic revision EVI broadened its scope and since has built a vaccine portfolio that addresses critical challenges and opportunities in vaccine R&D for a variety of diseases of poverty and emerging infectious diseases.

Currently EVI’s vaccine portfolio comprises around 20 vaccine candidates at different stages of development between late preclinical and mid-stage clinical development. In order to estimate future financing needs required for delivering the EVI portfolio and the potential public health impact of product launches, we conducted an analysis of EVI’s vaccine candidate portfolio using the P2I tool.

Together with similar pipeline portfolio reviews using the P2I tool that are currently being conducted by other product development partnerships (PDPs), the results will inform product developers as well as funders and policy makers regarding future funding needs. The results may also guide future investment priorities to maximise the chances of developing products for diseases that are missing urgently needed health products.

Methods

In this section, we describe the four key steps in this analysis, which are summarized in Figure 1. We do not describe the development of the first version of the P2I tool itself (P2I version 1, or P2I v.1), because this has been previously published. The development of a second version of the P2I tool, called P2I version 2 (P2I v.2), has also been previously described. In brief, the model is based on assumptions for costs per phase, attrition rates (probability of success) per phase, and cycle times per phase for four development phases (preclinical to phase III) for 11 different kinds of medical products, called archetypes. The P2I tool is a Microsoft Excel based tool and P2I v.2 uses Microsoft Excel 2016.

Step 1: review of EVI’s portfolio and classification of vaccine candidates into archetypes

The first step was to review, organize, and classify the vaccine candidates to allow them to be entered into the P2I model. To
enter candidates into the model, we needed to include (a) the target disease, (b) the current phase of development (the model assumes that the candidate is at the start of that phase), and (c) the archetype. Table 1 summarizes the vaccine candidates included in the analysis. Since all product archetypes were vaccines, we used the archetype classification from the P2I v.2 model (Table 2), in which candidates are classified as simple, complex, or unprecedented.

**Step 2: modeling of costs to move candidates through pipeline and likely launches, using P2I v.2 model with existing assumptions**

Once EVI’s portfolio of candidates was classified into archetypes (see Table 1), we then entered them into the P2I v.2 model and ran the model. In this first run of the model, we used exactly the same assumptions on cycle time, cost, and attrition rate per phase as in the P2I v.2 model. These assumptions are shown in Table 3. The assumptions were derived from three sources: the P2I model (shown in orange in Table 3), the McKinsey Risk-Adjusted Portfolio (RAP) Model (shown in yellow), and the Bill & Melinda Gates Foundation (shown in blue). The model outputs were the estimated costs to move the current candidates through the pipeline and the estimated number of launches.

**Step 3: modeling of costs to move candidates through pipeline and likely launches, using the P2I v.2 model with modified assumptions**

As a third step, we did a second run of the model after making selected modifications to some of the assumptions used in P2I v.2. EVI has collected data on its own parameters for cycle times, attrition rates, and costs per phase, which are shown in Table 4. We wanted to assess what effect the use of EVI’s parameters would have upon the outputs of the P2I model, but we recognized that many of these parameters were based on only two or three data points and were thus unreliable. For the second run of the model, we therefore made a pragmatic decision to use only those EVI parameters that were based on 10 data points, i.e. EVI’s parameters on success rate in phase 1 and the duration of phase 1. Thus, in the second run of the model, we made two modifications:

- Instead of using a success rate of 50% for phase 1 for unprecedented vaccines (the assumption in P2I v.2, as shown in Table 3), we used EVI’s success rate of 70% (see Table 4).
- Instead of using a phase length of 2 years for phase 1 for unprecedented vaccines (the assumption in P2I v.2,
### Table 2. Classification of vaccine candidates into archetypes (based on references 1 and 2; published under CC-BY 4.0).

<table>
<thead>
<tr>
<th>Archetype</th>
<th>Original description from P2I v.1</th>
<th>Examples</th>
<th>Additional description from P2I v.2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple vaccine</td>
<td>Platform has been used to develop other vaccines</td>
<td>Hep A, Hep B, polio, killed or live attenuated vaccines</td>
<td>Any vaccine platform that has been extensively researched and approved for use in the past. Pathogen has readily-identifiable vaccine targets that lack complexity. Conferral of immunity against disease-causing microorganism is expected as natural immunity to the pathogen is protective. Platform is likely to elicit robust protective response.</td>
</tr>
<tr>
<td>Complex vaccine</td>
<td>Requires completely novel approach; no platform; no existing research</td>
<td>Pneumococcal conjugate vaccine, meningitis B, DNA or mRNA vaccines</td>
<td>Any vaccine platform that requires a novel approach that has not been successfully approved for use in the past. Conferral of immunity against disease-causing microorganism is difficult to induce and maintain and natural immunity is not protective against reinfection. Platform may elicit incomplete/insufficient immunity and require boosting over time.</td>
</tr>
<tr>
<td>Unprecedented vaccine</td>
<td>Was not included as an archetype in P2I v.1</td>
<td>HIV, TB, malaria vaccines</td>
<td>All vaccine candidates for HIV, TB, and malaria are classified as “unprecedented” due to much higher attrition rates at phases II and III than other complex vaccines</td>
</tr>
</tbody>
</table>

### Table 3. Assumptions on costs, cycle times, and probabilities of success per phase for simple, complex, and unprecedented vaccines from the P2I v.2 model. This table is adapted from reference 2 under a CC-By 4.0 license.

<table>
<thead>
<tr>
<th>Archetype</th>
<th>Cost per phase ($, millions)</th>
<th>Length of phase (years)</th>
<th>Probability of success (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preclinical</td>
<td>Phase 1</td>
<td>Phase 2</td>
</tr>
<tr>
<td>Simple vaccine</td>
<td>6.7</td>
<td>2.2</td>
<td>13.2</td>
</tr>
<tr>
<td>Complex vaccine</td>
<td>16.6</td>
<td>2.5</td>
<td>13.9</td>
</tr>
<tr>
<td>Unprecedented vaccine</td>
<td>16.6</td>
<td>2.5</td>
<td>13.9</td>
</tr>
</tbody>
</table>

**Source of data for assumptions:**
- P2I model assumptions
- McKinsey RAP
- Bill & Melinda Gates Foundation

### Table 4. EVI’s own data on costs, cycle times, and probabilities of success per phase (see Appendix 1 for additional details).

<table>
<thead>
<tr>
<th>Stage</th>
<th>n=</th>
<th>Average value</th>
<th>Vaccine archetypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical phase duration (months)</td>
<td>2</td>
<td>36</td>
<td>all unprecedented</td>
</tr>
<tr>
<td>Preclinical phase cost EUR</td>
<td>3</td>
<td>EUR 2,483,333</td>
<td>1 simple, 2 unprecedented</td>
</tr>
<tr>
<td>Technical success phase I</td>
<td>10</td>
<td>100%</td>
<td>all unprecedented</td>
</tr>
<tr>
<td>Phase transition success phase I</td>
<td>10</td>
<td>70%</td>
<td>all unprecedented</td>
</tr>
<tr>
<td>Duration phase I (months)</td>
<td>10</td>
<td>17.4</td>
<td>all unprecedented</td>
</tr>
<tr>
<td>Phase I cost EUR</td>
<td>3</td>
<td>EUR 1,500,000</td>
<td>all unprecedented</td>
</tr>
<tr>
<td>Technical success phase II</td>
<td>2</td>
<td>100%</td>
<td>all unprecedented</td>
</tr>
<tr>
<td>Phase transition success phase II</td>
<td>2</td>
<td>100%</td>
<td>all unprecedented</td>
</tr>
<tr>
<td>Duration phase II (months)</td>
<td>2</td>
<td>22.5</td>
<td>all unprecedented</td>
</tr>
</tbody>
</table>
as shown in Table 3), we used EVI’s phase length of 1.45 years or 17.4 months (see Table 4).

For the EVI parameters that were included in the second run of the model, we used the following definitions:

- **Success rate**: EVI uses two different measures: (i) *technical success*: a clinical trial is considered successful if it concluded without being terminated prematurely for whatever reason, and (ii) *phase transition success*: a clinical trial is considered successful if after completion of the trial a decision is made to move to a subsequent clinical trial (even if no funding is available to do so; successful in this sense means also if you conduct, for example, another phase I clinical trial of the same antigen with a different formulation, dose, or age group).

- **Clinical trial duration**: EVI excludes clinical trial preparation, including dossier preparation and waiting for approval, in the duration. The duration is the period between the start and completion times. The start time is the time point when the clinical study opened for recruitment of participants, or the actual date on which the first participant was enrolled. The completion time is the time point when the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome.

**Step 4: sensitivity analysis**
As a final step, we conducted a sensitivity analysis, using an approach developed by Mestre-Ferrandiz et al. at the United Kingdom Office of Health Economics. We examined the impact of changing all probabilities of success per phase to 10% higher and 10% lower, and all costs per phase to 10% higher and lower. We also examined the impact of all possible combinations of these changes (e.g., 10% higher probability of success per phase and a 10% higher cost per phase, 10% higher probability of success per phase and a 10% lower cost per phase, etc.). We conducted this sensitivity analysis for both runs of the model.

**Results**

(i) Review of EVI’s portfolio
A review of EVI’s portfolio identified a total of 18 vaccine candidates under development, which were entered into the P2I v.2 model (Table 1). There were 8 candidates for malaria, 5 for placental malaria, 2 for leishmaniasis, and one each for shigellosis, Nipah virus, and Zika virus. Three candidates were in the pre-clinical phase, 11 in phase I, and 4 in phase II. There were no candidates in phase III. Among the 18 candidates, 15 were classified as unprecedented vaccines, 2 as simple vaccines, and one as a complex vaccine.

As described in the Methods section above, we first ran the model using the assumptions included in the P2I v.2 model. The results of this first run are described in section (ii) below. We then re-ran the model with some modifications to the assumptions that were made by EVI, based on EVI’s own historical data; section (iii) describes the results of this second run. Finally, we conducted a sensitivity analysis around the results of both runs of the model; the results of these sensitivity analyses are in section (iv).

(ii) First run of the P2I financing modeling tool, using assumptions from P2I v.2

**Estimated costs to move candidates through the pipeline.** The total estimated cost to move the 18 candidates along the pipeline to launch would be about US $470 million (Table 5, Figure 2). Just over one third (35%) of the expected costs would be incurred by development of the 8 vaccine candidates for malaria. Development of candidates for placental malaria, Nipah virus, and Zika virus would each account for about 16% of the total costs. The remaining costs would be for development of candidates for leishmaniasis (10% of costs) and shigellosis (7% of costs).

**Expected launches.** Overall, for all 18 candidates under development, the P2I model estimates that there would be 0.69 cumulative expected launches (we have left all results unrounded). Figure 3 summarizes the expected launches by disease. Table 6 summarizes the estimated cumulative launches by year from 2019-2031 alongside cost estimates. Figure 4 shows the time trends in cumulative costs and cumulative launch probability from 2019-31.

(iii) Second run of the P2I financing modeling tool, with modifications of selected assumptions
The re-run (second run) of the model using the modified assumptions increased the projected portfolio costs by US $46 million, bringing the total cost estimate to US$ 517 million to move all 18 candidates through the pipeline. The changes in estimated cost are driven by the increase in expected costs for the unprecedented vaccine candidates, i.e., the 8 malaria vaccine candidates, 5 placental malaria vaccine candidates and 2 leishmaniasis vaccine candidates. The remaining candidates for Nipah virus, Zika virus, and shigellosis were not affected by the change in parameters.

**Table 5. Cumulative cost and launch probability per disease based on P2I v.2 model projections.**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cost (US$, millions)</th>
<th>Cumulative expected launches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>165.62</td>
<td>0.098</td>
</tr>
<tr>
<td>Leishmaniasis</td>
<td>47.77</td>
<td>0.02</td>
</tr>
<tr>
<td>Shigellosis, ETEC</td>
<td>33.96</td>
<td>0.07</td>
</tr>
<tr>
<td>Nipah</td>
<td>73.96</td>
<td>0.22</td>
</tr>
<tr>
<td>Zika</td>
<td>73.96</td>
<td>0.22</td>
</tr>
<tr>
<td>Placental malaria</td>
<td>75.08</td>
<td>0.05</td>
</tr>
<tr>
<td>Total</td>
<td>470.35</td>
<td>0.69</td>
</tr>
</tbody>
</table>
Figure 2. Cost for vaccine development to launch by disease.

<table>
<thead>
<tr>
<th>Year</th>
<th>Cost (US$, millions)</th>
<th>Expected number of launches</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019</td>
<td>44.11794</td>
<td>0</td>
</tr>
<tr>
<td>2020</td>
<td>90.39988</td>
<td>0</td>
</tr>
<tr>
<td>2021</td>
<td>145.5832</td>
<td>0</td>
</tr>
<tr>
<td>2022</td>
<td>199.9804</td>
<td>0</td>
</tr>
<tr>
<td>2023</td>
<td>285.8381</td>
<td>0</td>
</tr>
<tr>
<td>2024</td>
<td>373.1006</td>
<td>0</td>
</tr>
<tr>
<td>2025</td>
<td>413.073</td>
<td>0.44</td>
</tr>
<tr>
<td>2026</td>
<td>437.6135</td>
<td>0.52</td>
</tr>
<tr>
<td>2027</td>
<td>459.6735</td>
<td>0.52</td>
</tr>
<tr>
<td>2028</td>
<td>465.4747</td>
<td>0.67</td>
</tr>
<tr>
<td>2029</td>
<td>467.4339</td>
<td>0.67</td>
</tr>
<tr>
<td>2030</td>
<td>469.3932</td>
<td>0.67</td>
</tr>
<tr>
<td>2031</td>
<td>470.3567</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Table 6. Cost and annual launch probability by year.

With regards to the expected number of launches, in the re-runs of the model, the launch probability increased for malaria, placental malaria, and leishmaniasis vaccines:

- For malaria, the estimate of expected launches increased from 0.098 to 0.11
- For placental malaria, the estimate of expected launches increased from 0.05 to 0.07
- For leishmaniasis, the estimate of expected launches increased from 0.024 to 0.03.

Table 7 provides a comparative summary of the costs and launch probabilities for each run of the model.

(iv) Sensitivity analyses for both runs of the model
We conducted a sensitivity analysis for the first and second runs of the model.

Sensitivity analysis for first run of the model. In the sensitivity analysis for the first run of the model (which used assumptions...
from P2I v.2), we found that the total estimated costs ranged from US$ 482.48 million to US$ 581.9 million (Table 8). The launch probability ranged from 0.53 to 0.96.

Sensitivity analysis for second run of the model. In the second sensitivity analysis for the second run of the model (which used modified assumptions), we found that the total estimated cost ranged from US$ 417.08 million to US$ 528.11 million (Table 9). The launch probability ranged from 0.51 to 0.91.

Conclusions and discussion
The mission of EVI is to accelerate the development of vaccines for diseases of poverty and emerging infectious diseases. Compared to other PDPs with a narrower focus, for example on a single disease, EVI has a broader scope and consequently a more heterogeneous portfolio, currently comprising 18 active vaccine candidates covering five different diseases/pathogens (malaria, including placental malaria, leishmaniasis, shigella/ETEC, Nipah and Zika viruses). An analysis of EVI’s current vaccine portfolio—providing estimations for future vaccine development costs and expected product launches—was considered important to inform EVI’s decision-making and priority setting, as well as to provide valuable information to global health funders and policy makers.

Overall, using the pre-defined assumptions established in the P2I tool, our modelling resulted in a total estimated cost of about US $470 million for moving all 18 candidates included in the analysis along the pipeline until launch. Of this total amount, just over one third (35%) of the expected costs would be incurred by the development of the eight vaccine candidates for malaria (excluding those for placental malaria). Development of the candidates for placental malaria, Nipah virus, and Zika virus would account for about 16% each of the total costs. The remaining financing would be required for the development of candidates for leishmaniasis and shigellosis (10% and 7% of total costs, respectively).

The re-run (second run) of the P2I model using modified assumptions for phase costs and length based on EVI’s internal data
increased the projected portfolio costs by US $46 million up to a total cost of US$ 517 million for all 18 candidates. The main driver of this change in the estimated cost is the increase in expected costs for the unprecedented vaccine candidates (i.e. the eight malaria vaccine candidates, five placental malaria vaccine candidates and two leishmaniasis vaccine candidates). Results for the vaccine candidates for Nipah virus, Zika virus, and shigellosis, ETEC were not affected by the change in these parameters.

The costs that we estimated using the P2I tool are likely to be an underestimate of the true costs. Vaccine development is a reiterative process, meaning that many steps, such as clinical trial phases, will be conducted several times. This process is in contrast to the rationale of the P2I tool, which assumes a straightforward development of product candidates without the reiteration of any particular development steps. For example, very often several phase I trials for a particular antigen are conducted, i.e. multiple trials in which different formulations, different routes of administration or different technology platforms for antigen presentation are being tested and compared. Also, very often several phase I clinical trials are conducted in which a vaccine’s safety is assessed in various age groups in an

### Table 8. Results of the sensitivity analysis for first run of the model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Percentage change from baseline</th>
<th>Effect on estimated cost of development</th>
<th>Effect on estimated number of product launches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of success</td>
<td>Low (-10%)</td>
<td>482.48</td>
<td>-6.60</td>
</tr>
<tr>
<td></td>
<td>High (+10%)</td>
<td>516.57</td>
<td>-0.72</td>
</tr>
<tr>
<td>Average cost per phase</td>
<td>Low (-10%)</td>
<td>464.91</td>
<td>-10.00</td>
</tr>
<tr>
<td></td>
<td>High (+10%)</td>
<td>482.48</td>
<td>-6.60</td>
</tr>
<tr>
<td>Probability of success, and average cost per phase</td>
<td>Low (-10% for both parameters)</td>
<td>410.7</td>
<td>-20.5</td>
</tr>
<tr>
<td></td>
<td>Intermediate 1 (Cost+10%, Probability of success -10%)</td>
<td>501.9</td>
<td>-2.8</td>
</tr>
<tr>
<td></td>
<td>Intermediate 2 (Cost-10%, Probability of success +10%)</td>
<td>523.7</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>High (+10% for both parameters)</td>
<td>640.1</td>
<td>23.91</td>
</tr>
</tbody>
</table>

### Table 9. Results of the sensitivity analysis for second run of model.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Percentage change from baseline</th>
<th>Effect on estimated cost of development</th>
<th>Effect on estimated number of product launches</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability of success</td>
<td>Low (-10%)</td>
<td>417.08</td>
<td>-11.33</td>
</tr>
<tr>
<td></td>
<td>High (+10%)</td>
<td>528.11</td>
<td>12.28</td>
</tr>
<tr>
<td>Average cost per phase</td>
<td>Low (-10%)</td>
<td>464.91</td>
<td>-1.16</td>
</tr>
<tr>
<td></td>
<td>High (+10%)</td>
<td>517.39</td>
<td>10.00</td>
</tr>
<tr>
<td>Probability of success, and average cost per phase</td>
<td>Low (-10% for both parameters)</td>
<td>410.7</td>
<td>-12.7</td>
</tr>
<tr>
<td></td>
<td>Intermediate 1 (Cost+10%, Probability of success -10%)</td>
<td>501.9</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>Intermediate 2 (Cost-10%, Probability of success +10%)</td>
<td>458.8</td>
<td>-2.5</td>
</tr>
<tr>
<td></td>
<td>High (+10% for both parameters)</td>
<td>580.9</td>
<td>23.51</td>
</tr>
</tbody>
</table>
age-deescalating manner (i.e., the vaccine is tested consecu-
tively in volunteer groups with decreasing age). It is therefore
rather unlikely that any vaccine candidate would immediately
advance to a phase II clinical trial after the conduct of a
single phase I clinical trial only. Consequently, the total costs
for the development of the different vaccine candidates in
EVI’s portfolio are likely to be significantly higher than those
estimated by the P2I tool. In addition, as several phase I or
phase II clinical trials are likely to be conducted for the same
vaccine (as explained above), due to such “reiterated”
phases the overall timelines to reach the market are expected
to be longer.

With regards to the estimated future launches, for all 18 can-
didates under development, the P2I model estimates that there
would be 0.69 cumulative expected launches. In the re-run
of the model using EVI’s own internal parameters, thanks to
higher success rates at EVI as compared to the P2I tool’s prede-
ned parameters, the launch probability increased for malaria,
placental malaria, and leishmaniasis vaccines (from 0.098 to
0.11, from 0.05 to 0.07, and from 0.024 to 0.03, respect-
ively). Directly related to this increased launch probability,
the total estimated costs for moving these vaccine candidates
through the pipeline increased accordingly. This difference
between the estimated future product launches emphasizes that,
in order to increase the chances of ultimate success with this
kind of product development, it is important to make the prod-
uct development process technically as efficient as possible,
(i.e., reducing the attrition rates as much as possible. If
attrition rates during product development cannot be reduced,
the only other chance of achieving ultimate product launches is
to boost the overall number of product candidates in the pipeline,
obviously in the end resulting in higher total costs linked to the
launch of a single product due to the high costs linked to failed
product candidates.

However, rather than looking at the isolated results on
likely launches from the analysis of a single organization’s
portfolio, a more meaningful estimation will be obtained by
conducting a much wider portfolio analysis in which the launch
estimation results of the entire global vaccine candidate portfo-
lio are estimated in an integrated, combined manner. Only this
kind of “full portfolio” study can provide a reliable predic-
tion of the product success rates on a global level for the
next few decades.

The P2I tool has a number of other limitations, which were
described in detail by Young et al. These include: (i) as a static,
deterministic model, it does not take into account possible
improvements in product development techniques over time (e.g.
R&D efficiencies that reduce costs); (ii) the model’s assump-
tions for costs, attrition rates, and cycle times for phase are based
on product development data from across multiple diseases
(including non-communicable diseases—the model does
not reflect possible differences in R&D parameters between
different diseases); and (iii) the model does not include all
phases of development (e.g. it excludes drug discovery, basic
research, and regulatory review).

In this study, several adaptations to the P2I tool initially were
considered with the aim of improving the tool’s usefulness
and reliability. First, we considered making adaptations of the
assumptions for success rates, costs and cycle times based
on EVI’s longstanding experience with conducting studies in
resource-limited, low-income settings. Second, we consid-
ered making adaptations for the same parameters based on
(a) the fast-track clinical development strategy often used by EVI
(consisting of a strategy in which the first-in-human evalua-
tion involves a staggered multi-centre phase Ia/b clinical trial
resulting in shorter timelines8), and (b) the inclusion of accel-
erated clinical testing based on controlled human infection
models available, for example, for malaria8. Third, in the
original proposal we considered including adaptations of the
assumptions for costs and cycle times for vaccines that
might be eligible for accelerated approval by regulatory
authorities, for example the “Expedited Programs for Serious
Conditions—Drugs and Biologics” from the US Food and Drug
Administration9.

In the end, we were able to do one re-run of the P2I model
using EVI’s own parameters for success rates and cycle times
for phase I clinical trials for unprecedented vaccines (70% and
17.4 months, respectively, compared to 50% and 24 months
defined in the original P2I tool for unprecedented vaccines).
However, although to date EVI has been involved in the con-
duct of over 30 clinical trials, data from only a limited number
of studies could be used in the analyses conducted. When it came
to estimating clinical trial costs, for example, for several trials
it was not possible to extract the specific costs for preclinical
or clinical trial activities out of the overall study costs.

Concerning the proposed modification of P2I parameters based
on accelerated clinical testing using controlled human chal-
genle models and on accelerated approval by regulators, we
realized that although these two issues are likely to speed up
vaccine development, currently there is not enough evidence/
data based on which the P2I parameters could be adapted and
analyses be run to assess their impact.

In conclusion, we found that despite the limitations dis-
cussed above, the P2I tool was flexible and adaptable enough
to be used to study EVI’s portfolio. We believe that the P2I
model represents a useful tool to analyze the portfolio of
global health products under development. We expect that
studies like ours will inform future updates of the model
that will further increase its value for product developers,
R&D funders, and decision makers.

**Data availability**

All data underlying the results are available as part of the article
and no additional source data are required.
The particular vaccine candidates included in this study have been anonymized for intellectual property reasons.

Grant information
This work, Project ID Nº B80106, received financial support from TDR, the Special Programme for Research and Training in Tropical Diseases, co-sponsored by UNICEF, UNDP, the World Bank and WHO.

The funders had no role in the study design, data collection, analysis, decision to publish, or preparation of the manuscript.

Acknowledgments
We would like to thank Robert Terry at TDR for his guidance on this study.

References


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