Accelerating vaccine innovation for emerging infectious diseases via parallel discovery

Joseph Barberio, Jacob Becraft, Zied Ben Chaouch, Dimitris Bertsimas, Tasuku Kitada, Michael L. Li, Andrew W. Lo, Kevin Shi, Qingyang Xu

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May 3, 2022
The Business of Vaccines

- Business model for vaccines is challenging
- Non-profits like CEPI, WHO, CARB-X, Gates Foundation are helping
- But philanthropy is not enough
- Is it possible to attract more private-sector investment to address emerging infections diseases?
Sharpe Ratio $\equiv \frac{E[R] - R_f}{SD[R]}$
Would You Invest In This Project?

- $200MM investment, 10-year horizon
- Probability of positive payoff is 5%
- If successful, annual profits of $2B for 10 years

- \[ E[R] = 11.9\% \]
- \[ SD[R] = 423.5\% \]
- \[ SR = 0.03 \]
What If We Invest In 150 Programs Simultaneously?:

- Requires $30B of capital
- Assume programs are IID (can be relaxed)
- Diversification changes the economics of the business:

\[
\mathbb{E}[R] = 11.9\% \\
SD[R] = \frac{423.5\%}{\sqrt{150}} = 34.6\% \implies SR = 0.33
\]
- But can we really raise $30B??
- It depends on the portfolio’s risk/reward profile (correlations?)

Financial Engineering Can Help

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Challenges of Vaccine Development

Why did big pharma leave vaccine development (before the COVID-19 pandemic)?

Plotkin et al. (2015):

- Declining and highly uncertain revenues
- Lack of funding in the absence of an imminent threat
- Vaccines for uncommon but deadly infectious diseases are not as profitable as the seasonal flu
Challenges of Vaccine Development

How has the pandemic changed vaccine development?

- **Innovations** in biomedical technology (e.g., mRNA vaccines)
- Unprecedented acceleration for **clinical development**
- Unprecedented **collaboration** among stakeholders
- Increased **public awareness** of the importance to prevent future pandemic outbreaks of emerging infectious diseases (EID)
Investment Pop Quiz #3

Would You Invest In This Project?

- $200M investment, 1-year horizon
- Probability of success is 25%
- If successful, $187.3M = PV_{20}(10\% \times $20/dose \times 10M)

SR = ???

**Diagram:**
- Total Cost:
  - $200M
- $20M, $20M...
- Year 0, 1, 20
- Present Value of Earnings: $187.3M
- Price doses, prob. of outbreak

Computation:

\[
R = \frac{97.7}{200} - 0.064 = 0.01
\]
Simulating a Vaccine Fund

- Adapted from CEPI and Vu et al. (2022)
- 10 vaccine candidates for “disease X” (pandemic)
- Simulate outbreaks over 20 years

<table>
<thead>
<tr>
<th>Disease</th>
<th># Vaccine Candidates</th>
<th>Annual Probability of Outbreak (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease X</td>
<td>10</td>
<td>1.0</td>
</tr>
<tr>
<td>Chikungunya</td>
<td>16</td>
<td>10.8</td>
</tr>
<tr>
<td>Zika Virus</td>
<td>18</td>
<td>4.3</td>
</tr>
<tr>
<td>Lassa Fever</td>
<td>7</td>
<td>100.0</td>
</tr>
<tr>
<td>Rift Valley Fever</td>
<td>3</td>
<td>10.5</td>
</tr>
<tr>
<td>SARS-CoV-1</td>
<td>2</td>
<td>7.1</td>
</tr>
<tr>
<td>West Nile Virus</td>
<td>23</td>
<td>10.0</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>8</td>
<td>40.0</td>
</tr>
<tr>
<td>Crimean-Congo Hemorraghic Fever</td>
<td>7</td>
<td>12.5</td>
</tr>
<tr>
<td>Nipah Virus</td>
<td>20</td>
<td>15.8</td>
</tr>
<tr>
<td>Marburg Virus</td>
<td>6</td>
<td>12.0</td>
</tr>
</tbody>
</table>
Simulating a Vaccine Fund

- Simulate epidemics each year
- For each occurrence, follow flowchart
Simulating a Vaccine Fund

<table>
<thead>
<tr>
<th>Category</th>
<th>Item</th>
<th>Unit Cost (USD)</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed cost</td>
<td>Production line</td>
<td>$58M</td>
<td>1 bioreactor of 30L working volume</td>
</tr>
<tr>
<td>Variable costs</td>
<td>Raw materials</td>
<td>$456.6M/(year · production line)</td>
<td>29,162 grams of mRNA per production line per year</td>
</tr>
<tr>
<td></td>
<td>Consumables</td>
<td>$150M/(year · production line)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Labor</td>
<td>$20/hour</td>
<td>113,186 labor hours per production line per year</td>
</tr>
<tr>
<td></td>
<td>Quality control</td>
<td>$10/hour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fill-and-finish</td>
<td>$0.27/dose</td>
<td>10-dose vials</td>
</tr>
<tr>
<td></td>
<td>Lab, utility, waste</td>
<td>&lt;1% total cost</td>
<td>Not modeled here</td>
</tr>
<tr>
<td></td>
<td>management, etc.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sources: Kis & Rizvi (2021), Kis et al. (2021)
### Results

- Needs $9.5 billion to break even
- Prevents 31 epidemic outbreaks on average in the next 2 decades

<table>
<thead>
<tr>
<th>Metric</th>
<th>Mean</th>
<th>Std Dev</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Return (%)</td>
<td>−6.0</td>
<td>6.7</td>
<td>−5.7</td>
</tr>
<tr>
<td>NPV ($ billion)</td>
<td>−9.5</td>
<td>4.1</td>
<td>−9.9</td>
</tr>
<tr>
<td>Investment ($ billion)</td>
<td>17.7</td>
<td>5.3</td>
<td>17.8</td>
</tr>
<tr>
<td>Revenue ($ billion)</td>
<td>7.5</td>
<td>7.7</td>
<td>5.8</td>
</tr>
<tr>
<td>Profit ($ billion)</td>
<td>−10.0</td>
<td>7.4</td>
<td>−11.5</td>
</tr>
<tr>
<td># Epidemics Prevented</td>
<td>31</td>
<td>13</td>
<td>34</td>
</tr>
</tbody>
</table>
Results

Costs of Vaccine Development and Delivery

- 94% of costs are clinical trials (59% in Phase 3)
- mRNA technology does not save much in costs (but reduces time!)
Sensitivity Analysis: Price

- Expected annual return is **negative** unless price per dose > $69.00
- Expected NPV is **negative** unless the price per dose > $78.00
- 12 common adult vaccines have list prices above $100.00 in US*

<table>
<thead>
<tr>
<th>Price Per Dose</th>
<th>E[$R_a$]</th>
<th>SD[$R_a$]</th>
<th>E[NPV] ($B)</th>
<th>SD[NPV] ($B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$20.00 (baseline)</td>
<td>−6.0%</td>
<td>6.7%</td>
<td>−9.5</td>
<td>4.1</td>
</tr>
<tr>
<td>$69.00</td>
<td>0.0%</td>
<td>7.1%</td>
<td>−1.4</td>
<td>11.9</td>
</tr>
<tr>
<td>$78.00</td>
<td>0.7%</td>
<td>7.1%</td>
<td>0.0</td>
<td>13.5</td>
</tr>
<tr>
<td>$100.00</td>
<td>1.9%</td>
<td>7.2%</td>
<td>3.6</td>
<td>17.4</td>
</tr>
</tbody>
</table>

*US CDC (Jan. 1, 2022)
What Can Be Done?

- Pricing policy innovation:
  - AMCs, subscription model, etc.
- More generally, government policy is key
- Is healthcare a privilege or a right? Ethics?
- Should vaccine and anti-infective companies be considered "regulated utilities"?
- Finance can play a **positive** role in facilitating public health
What Can Be Done?

Government involvement is essential when:

1. The investment **horizon** is long (over a decade)
2. The **capital** required is significant (~ $200 million)
3. The **probability of success** is low (~ 25% overall)
4. Potential **benefits** to the society are large

- Risk-based “market failure” (Lo, 2022)

Sharpe Ratio = \[
\frac{\text{Private–Sector Reward}}{\text{Risk}}
\]
Thank You!
References

References

- Lo, AW, Siah, KW, Wong, CH. Estimating probabilities of success of vaccine and other anti-infective therapeutic development programs, Harvard Data Science Review 2020, COVID-19 Special Issue 1. [https://doi.org/10.1162/99608f92.e0c150e8](https://doi.org/10.1162/99608f92.e0c150e8).
- Lo, AW. Risk-based market failures and how to address them via financial contracting, MIT LFE working paper, 2022.
Supplementary Materials
Simulating a Vaccine Fund

- Probability of success (PoS)
- Correlation of trial outcomes
- Clinical trial duration and cost

### Probability of success (PoS)

<table>
<thead>
<tr>
<th>Param.</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PoS (%)</td>
<td>60.0</td>
<td>83.6</td>
<td>65.8</td>
<td>80.9</td>
</tr>
</tbody>
</table>

### Clinical trial duration (months)

| Duration (months) | 18.0 | 24.0 | 18.0 | 14.0 |

### Clinical trial cost ($ million)

| Cost ($ million) | 26.0 | 14.0 | 28.0 | 150.0 |

Correlation matrix of vaccine trial outcomes calibrated by biomedical similarity of pathogens

Gouglas et al., 2018; Project ALPHA, 2021

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Increasing probability of success for mRNA technology increases both the number of approved vaccines and total investment. Revenue of vaccine sales increases less significantly.

<table>
<thead>
<tr>
<th>Price Per Dose</th>
<th>$\alpha_{tech} = 1.0$</th>
<th>$\alpha_{tech} = 1.1$</th>
<th>$\alpha_{tech} = 1.2$ (baseline)</th>
<th>$\alpha_{tech} = 1.3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E[R_a]$</td>
<td>$-6.7%$</td>
<td>$-6.2%$</td>
<td>$-6.0%$ (baseline)</td>
<td>$-5.8%$</td>
</tr>
<tr>
<td>$SD[R_a]$</td>
<td>$11.9%$</td>
<td>$9.1%$</td>
<td>$6.7%$</td>
<td>$4.8%$</td>
</tr>
<tr>
<td>$E[\text{NPV}]$ ($B$)</td>
<td>$-8.1$</td>
<td>$-8.8$</td>
<td>$-9.5$</td>
<td>$-9.9$</td>
</tr>
<tr>
<td>$E[\text{Inv}]$ ($B$)</td>
<td>$15.2$</td>
<td>$16.4$</td>
<td>$17.7$</td>
<td>$18.7$</td>
</tr>
</tbody>
</table>
Estimation of clinical trial success rates and related parameters

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SUMMARY

Previous estimates of drug development success rates rely on relatively small samples from databases curated by the pharmaceutical industry and are subject to potential selection biases. Using a sample of 406,038 entries of clinical trial data for over 21,143 compounds from January 1, 2000 to October 31, 2015, we estimate aggregate clinical trial success rates and durations. We also compute disaggregated estimates across several trial features including disease type, clinical phase, industry or academic sponsor, biomarker presence, lead indication status, and time. In several cases, our results differ significantly in detail from widely cited statistics. For example, oncology has a 3.4% success rate in our sample vs. 5.1% in prior studies. However, after declining to 1.7% in 2012, this rate has improved to 2.5% and 8.3% in 2014 and 2015, respectively. In addition, trials that use biomarkers in patient-selection have higher overall success probabilities than trials without biomarkers.
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#### Table 2. The POS by therapeutic group, using data from January 1, 2000, to October 31, 2015. We computed this using the path-by-path method. SE denotes the standard error.

<table>
<thead>
<tr>
<th>Therapeutic group</th>
<th>Phase 1 to Phase 2</th>
<th>Phase 2 to Phase 3</th>
<th>Phase 3 to Approval</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total paths</td>
<td>POS</td>
<td>(SE, %)</td>
<td>Total paths</td>
</tr>
<tr>
<td>Oncology</td>
<td>17368</td>
<td>57.6</td>
<td>(0.4)</td>
<td>6533</td>
</tr>
<tr>
<td>Metabolic/</td>
<td>3589</td>
<td>76.2</td>
<td>(0.7)</td>
<td>2357</td>
</tr>
<tr>
<td>Endocrinology</td>
<td>(0.7)</td>
<td>(0.7)</td>
<td>(0.9)</td>
<td>(0.9)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2810</td>
<td>73.3</td>
<td>(0.8)</td>
<td>1858</td>
</tr>
<tr>
<td>CNS</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(0.8)</td>
<td>(1.1)</td>
</tr>
<tr>
<td>Autoimmune/</td>
<td>5086</td>
<td>68.9</td>
<td>(0.6)</td>
<td>2910</td>
</tr>
<tr>
<td>Inflammation</td>
<td>(0.6)</td>
<td>(0.6)</td>
<td>(0.6)</td>
<td>(0.9)</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>757</td>
<td>78.7</td>
<td>(1.7)</td>
<td>475</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>3963</td>
<td>70.1</td>
<td>(0.9)</td>
<td>2314</td>
</tr>
<tr>
<td>Ophthalmology</td>
<td>674</td>
<td>87.1</td>
<td>(1.3)</td>
<td>461</td>
</tr>
<tr>
<td>Vaccines (Infectious Disease)</td>
<td>1869</td>
<td>76.8</td>
<td>(1.0)</td>
<td>1235</td>
</tr>
<tr>
<td>Overall</td>
<td>41040</td>
<td>66.4</td>
<td>(0.2)</td>
<td>21180</td>
</tr>
<tr>
<td>All without oncology</td>
<td>23672</td>
<td>73.0</td>
<td>(0.3)</td>
<td>14647</td>
</tr>
</tbody>
</table>

**Average POS:** 3.4% (SE: 0.3%)
Vaccine Success Rates

Estimating Probable Success of Vaccines and Other Anti-Infective Therapeutic Development Programs

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