OPEN LETTER

Adopting a logical framework model to help achieve a balanced and healthy vaccine R&D portfolio [version 1; peer review: 1 approved]

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Abstract

Vaccines are currently the 5th biggest therapy area with global sales for prophylactic and therapeutic vaccines to be ~ $30B, which is expected to increase to $45B by 2024. Immunization is globally recognized as one of the best investments to improve health, with impact lasting beyond saving 2-3M lives every year with benefits accrued over a lifetime.

Enterprise value of any R&D company is a cumulative sum of its projects and proprietary technologies. Hence organizations need to continuously evaluate their portfolios to review the health of projects as changes in external environment may impact project viability. Simultaneously, addition of any new project in a company’s portfolio is a significant investment and needs to be evaluated using an objective multi-parametric framework. In this pursuit, Hilleman Labs, an equal joint venture by MSD and Wellcome Trust, has created a logical framework to evaluate potential vaccine candidates before they are added to the portfolio.

Keywords

Vaccine, R&D, framework, portfolio, health, portfolio health, logical, Hilleman, evaluation framework

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Author roles: Lalani B: Conceptualization, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; Sobti S: Conceptualization, Methodology, Validation, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

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Introduction
Vaccines are currently the 5th biggest therapy area with global sales for prophylactic and therapeutic vaccines ~ $30B, which is expected to increase to ~$45B by 2024. Immunization is globally recognized as one of the best investments to improve health, with impact lasting much beyond saving 2-3M lives every year with benefits accrued over a lifetime. This increase is due to inclusion of new vaccines in the Expanded Program of Immunization, especially in low- and middle-income countries supported by the Global Alliance for Vaccines and Immunization (Gavi) and global stakeholders, such as Bill & Melinda Gates Foundation, World Health Organization and United Nations International Children’s Emergency Fund (UNICEF). In addition, increasing acceptance of the role of vaccines to fight pandemics and other infections, and reducing anti-microbial resistance (AMR), is also driving the growth of vaccine usage worldwide.

Given the importance of vaccines in improving public health, there are over 70 private, non-profit and public sector companies currently engaged in human vaccine development, with all firms having an appreciation that any new project/product they embark upon will require a gestation period of 10–12 years from laboratory to licensure. Research involving novel products is iterative, requires significant investment and needs to account for attrition. A recent study pegs the cost of taking a biopharmaceutical from pre-clinical stage to licensure at $125M, with another estimating the risk adjusted cost of R&D between USD $130-350M. A more inclusive study by Tufts University estimates the out-of-pocket costs for development of a New Molecular Entity as ~ $1.4B.

Enterprise value of any R&D company is a cumulative sum of its projects and proprietary technologies. Hence organizations need to continuously evaluate their portfolios to review the health of projects as changes in external environment may impact project viability. Simultaneously, addition of any new project in a company’s portfolio is a significant investment and needs to be evaluated using an objective multi-parametric framework. In this pursuit, Hilleman Labs, an equal joint venture by MSD and Wellcome Trust in 2009, headquartered in New Delhi, India. Hilleman Laboratories is a global vaccine R&D organization committed to developing high impact, affordable vaccines for low- and middle-income countries. Our translational research focuses on creating safe, low-cost vaccines and innovative delivery technologies that are highly effective and can be easily incorporated into immunization programs. Hilleman Lab’s focus is on transforming ideas into products and technologies through translational R&D and by building partnerships with global stakeholders and vaccine manufacturers.

Approach to creating the framework
Like most products and services, vaccine R&D candidates should be evaluated based on a series of internal and external factors that help an organization assess whether the molecule is in-line with the organization’s strengths, along with being relevant to the marketplace in the future.

A literature search was conducted to review and understand bio-pharma industry best practices to adding a new molecule in pipeline. We used key words such as “Vaccine research portfolio”, “vaccine R&D”, “vaccine portfolio”, and “portfolio management” etc. on databases available at Wellcome Open Research and Google. We also leveraged the vaccine investment strategy framework used by Gavi2 for selecting new vaccines to include in its portfolio, and perused strategic plans for public health institutes, such as Johns Hopkins Medicine, to gather information pertaining to industry practices.

The strategy team leveraged internal learning in terms of portfolio health evaluation and optimization to identify the factors important for Hilleman Lab’s performance and success. A cross-functional team, consisting of internal team leads for R&D, business development, manufacturing, quality and compliance, was constituted and convened to seek feedback on the framework to ensure the framework is comprehensive, objective and inclusive. The feedback cycle was a 2-step process. We developed a first draft of the framework, which was introduced to the team leaders in a meeting. There was a detailed discussion regarding inclusion/exclusion of parameters outlined in the draft framework. The weightage assigned to each individual factor was discussed to incorporate diverse points of view and make the framework adaptable by a wider audience within the organization.

The logical framework was then further refined and validated by utilizing data shared for potential vaccine candidates by research and development teams for a myriad of factors listed in Table 1. Once the changes were made to the framework, another meeting was convened to present the final version and gain buy-in.

The logical framework can be further customized by organizations by incorporating/removing certain factors based on relevance. It is a two-step process that helps Hilleman Labs select a candidate(s) by eliminating potential candidates using a set of internal and external factors (Figure 1; Table 2). The process of finalizing internal and external factors was informed by various aspects of the business. For internal factors, we considered key strengths of a vaccine R&D organization, including Hilleman Labs. In addition, we also looked at factors critical to achieving efficiencies, i.e. reducing costs by limiting new investments, ability to utilize current infrastructure and leveraging partnerships and ensuring public health impact in line with Hilleman Labs mission and vision. For external factors, primary determinants of supply and demand were included. In addition, to address economic considerations, we included factors, such as number of competitors, vaccine pipeline and market pricing and technical feasibility.
Table 1. Logical Framework – Details.

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Internal Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 - High</td>
<td>2 - Medium</td>
</tr>
<tr>
<td>Key capabilities / research expertise / critical knowledge</td>
<td>• HL possesses technical expertise, critical knowledge and key capabilities (including trained staff, field of research) or has identified partner with these capabilities</td>
</tr>
<tr>
<td>Portfolio fit</td>
<td>• The candidate/technology is perfect fit with current research projects (enteric diarrheal diseases and conjugate vaccine platform)</td>
</tr>
<tr>
<td>Resource fit</td>
<td>• HL personnel are well-trained, experienced on the subject/topic of research</td>
</tr>
<tr>
<td>Personnel availability</td>
<td>• Well-trained personnel with technical expertise are available and have spare capacity</td>
</tr>
<tr>
<td>Ability to utilize current infrastructure</td>
<td>• Research does not require any change/addition to existing infrastructure (equipment, work space, etc.) / there is an identified partner with the required infrastructure</td>
</tr>
<tr>
<td>Leveraging partnerships</td>
<td>• HL will be able to leverage existing partnerships or has identified a partner, partner is/will be keen to collaborate</td>
</tr>
<tr>
<td>Public Health Impact</td>
<td>• There is a pressing public health need in high, middle- and low-income countries, HL should pursue irrespective of other factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Step 2</th>
<th>External Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 - High</td>
<td>2 - Medium</td>
</tr>
<tr>
<td>Mortality</td>
<td>• High disease burden in terms of overall mortality, mortality in children &lt;5 years</td>
</tr>
<tr>
<td>Morbidity</td>
<td>• High disease burden in terms of overall morbidity, QALY, etc.</td>
</tr>
<tr>
<td>Supply vs Demand</td>
<td>• Strong demand and less supply in the market, indicated by expected volume demand and anticipated revenue</td>
</tr>
<tr>
<td>No. of competitors</td>
<td>• No competitors in the market currently</td>
</tr>
</tbody>
</table>
### Step 2

**External Factors**

<table>
<thead>
<tr>
<th></th>
<th>3 - High</th>
<th>2 - Medium</th>
<th>1 - Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Pipeline</td>
<td>Few other molecules in pipeline, in initial stages of development, low IP restrictions</td>
<td>More than 4 molecules in pipeline, initial to advanced stages of development, moderate IP restrictions</td>
<td>Many molecules in pipeline, some in advanced stages, high IP restrictions</td>
</tr>
<tr>
<td>Market Pricing</td>
<td>High expected market pricing (hence, high revenue)</td>
<td>Moderate expected market pricing (hence, moderate revenue)</td>
<td>Low expected market pricing (hence, low revenue)</td>
</tr>
<tr>
<td>Technical Feasibility</td>
<td>The project feasibility is high, considering technical, regulatory, IP, vaccine design etc.</td>
<td>The project feasibility is medium considering technical, regulatory, IP, vaccine design etc.</td>
<td>The project feasibility is low, considering technical, regulatory, IP, vaccine design etc.</td>
</tr>
</tbody>
</table>

### Step 3

<table>
<thead>
<tr>
<th></th>
<th>3 - High</th>
<th>2 - Medium</th>
<th>1 - Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial Resistance</td>
<td>High risk of AMR</td>
<td>Medium risk of AMR</td>
<td>Low risk of AMR</td>
</tr>
<tr>
<td>Improving Health Equity</td>
<td>High impact on improving health equity</td>
<td>Medium impact on improving health equity</td>
<td>Low impact on improving health equity</td>
</tr>
<tr>
<td>Epidemic Potential</td>
<td>High epidemic potential</td>
<td>Medium epidemic potential</td>
<td>Low epidemic potential</td>
</tr>
</tbody>
</table>
The framework and how it works

Table 1 contains the detailed framework proposed.

Figure 1. Evaluation framework. The figure captures the underlying principles and working of the evaluation framework by identifying two primary filters applied as a part of the process.

### Table 2. Internal and external factors included in the framework.

<table>
<thead>
<tr>
<th>Internal Factors (Step 1)</th>
<th>External Factors (Step 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key capabilities / Research expertise / Critical knowledge</td>
<td>Mortality</td>
</tr>
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<tr>
<td>Resource Fit</td>
<td>Supply vs Demand</td>
</tr>
<tr>
<td>Resource Availability</td>
<td>Number of Competitors</td>
</tr>
<tr>
<td>Ability to Utilize Current Infrastructure</td>
<td>Vaccine Pipeline</td>
</tr>
<tr>
<td>Leveraging Partnerships</td>
<td>Market Pricing</td>
</tr>
<tr>
<td>Public Health Impact</td>
<td>Technical Feasibility</td>
</tr>
</tbody>
</table>

The process of finalizing internal and external factors was informed by various aspects of the business.

For internal factors, we considered key strengths of a vaccine R&D organization, including Hilleman Labs.

Organizational strengths: To develop a successful vaccine candidate, R&D organizations should first explore internal factors that are its established key strengths. We have classified the internal factors under the following 4 categories:

- **Knowledge**: Technical aspects such as key capabilities (e.g., vaccine platforms), research expertise and critical knowledge play an important role in developing a strong vaccine portfolio. Being able to rely on internal expertise by emulating past successes and further strengthening the portfolio can be an indicator of the potential of a vaccine candidate.

- **Resources**: The most important resource at an organization’s disposal is its people. Talented employees with technical know-how and the right skillset give a boost to the probability of success of any R&D project. Facilities and infrastructure are the tools that an organization equips its human resources with, to deliver value. If the new vaccine candidate under consideration does not require any incremental changes to the existing infrastructure, it leads to cost-saving by avoiding new investments, as well as time-saving by being able to initiate and undertake the project immediately.

- **Partnerships**: Vaccine research and development is a time and resource intensive process. By developing and leveraging collaborative partnerships, organizations can enhance the probability of success. An organization engaged in vaccine development would require productive partnerships with multiple organizations across the development lifecycle.

- **Vision/Mission**: An organization’s vision and mission ensures that the activities associated with developing the new vaccine candidate are in-line with the organization’s goals and will contribute in achieving those goals. For Hilleman Labs, being able to create public health impact by developing vaccines for low- and middle-income countries is a crucial part of what we do. As a result, “public
health impact” features as an internal factor for reviewing potential vaccine candidates.

Once the potential vaccine candidates have been evaluated based on the internal environment, in the second step we shift the focus to external factors impacting the outcome and uptake of a prospective vaccine. We have classified external factors under the following 3 categories:

- **Epidemiology:** Estimation of disease burden (morbidity, mortality etc.) is an important predictor of need for an intervention.

- **Market Landscape:** The interplay of supply vs demand, number of players in the market, number of candidates in the pipeline and expected unit price of the vaccine candidate play a crucial role in deciding economic success of a vaccine candidate. These are business considerations to guide management’s decision on adding a new candidate to the pipeline with a view to future sustainability.

- **Technical Feasibility:** This factor serves as the litmus test, as it is easy for teams to over-commit and embark on an overtly ambitious project. Hence this factor will reiterate that the potential new candidate is technically achievable.

For each of the internal and external factors, the evaluator is required to score the vaccine candidate as High (score=3), Medium (score=2) or Low (score =1). A clear definition of high, medium and low-ranking candidate is provided for all the factors to avoid subjective interpretation; with weights assigned to each internal and external factor to reflect relative importance. A candidate is evaluated against internal factors and a weighted average is calculated. Candidates with a weighted average above a threshold (0.5) progress to the next stage and are then assessed based on external factors. For details regarding the high, medium and low-ranking scores for all factors, please refer to Table 1.

At the end of Step 2, additional filters such as reducing AMR, improving health equity, epidemic potential, etc. are applied with only top 1 or 2 candidates being finally added to the portfolio. These additional filters are based on emerging public health trends, which can be addressed by availability of quality assured vaccines. These factors may evolve with time as new threats emerge, resulting in a change in global priorities.

The framework provides an objective definition of high, medium and low categories, which helps the evaluator refrain from using prior knowledge and biases while ranking the candidates. For example, the framework defines “high” public health impact as “There is a pressing public health need in high, middle- and low-income countries, organization should pursue irrespective of other factors”. Since the definition clearly emphasizes a pressing need in high-, middle- and low-income countries, the evaluator is not tempted to score high or low based on pressing need in a specific patient population versus wider global impact. A distinct definition of each of the internal and external factors is provided in the framework, which reduces any biases or prejudices.

**Validation of the framework**

To validate and refine the framework, we evaluated 6 potential vaccine candidates (A-F) using the framework. The first step eliminated 3 candidates based on internal factors and the remaining passed to stage 2 of evaluation based on external factors. Post the stage 2 review, one candidate emerged as the top choice, which was then included in company’s development portfolio. For details see Figure 2.

**Conclusion**

The pursuit of new products feels haphazard and sporadic for a vaccine research organization since the time from research to market is > 10 years. Thus it becomes critical for organizations to evaluate a myriad of factors before adding a project to their portfolio. A more balanced and healthier portfolio will have products that feature across the spectrum of the development lifecycle (i.e. a mix of early and late stage candidates). As companies strive to develop a robust pipeline of vaccines across many infectious disease targets, a common pitfall is that they may be spreading their resources too thin; with increasing complexity and rising costs of conducting clinical trials over the years. Also, as a large number of companies are chasing similar vaccine targets resulting in affordable and competitive pricing, it simultaneously poses pressure on companies to strive for lower cost of goods and overall company sustainability. Hence, it is critical for vaccine development companies to review and manage their portfolio by allocating resources differentially, while simultaneously terminating nonviable projects to ensure product relevance in the ever-evolving disease and global market landscape.
Data availability
No data is associated with this article.

Grant information
The author(s) declared that no grants were involved in supporting this work. However, this work was supported by Hilleman Labs, an equal joint venture between MSD and Wellcome Trust.

Acknowledgements
We are grateful to Dr. Davinder Gill for his critical review of the framework and this article. We would also like to acknowledge and thank entire Hilleman Labs team for their support and feedback.
References

Open Peer Review

Current Referee Status: ✔

Version 1

Referee Report 23 April 2019

https://doi.org/10.21956/wellcomeopenres.16549.r35219

Jayasree K. Iyer
Access to Medicine Foundation, Amsterdam, The Netherlands

The article is original and balanced in view. The authors have presented here a method, they have developed to assess the strength or "health" as they call it of a vaccine R&D portfolio. This is intended to be helpful for any organization, private or public in nature, to be able to evaluate the opportunity they have in addressing access while remaining a sustainable entity. In my view, this framework is indeed useful and will inform readers well. The paper is well aligned with today's needs and the international agenda on vaccines access.

A few suggestions to strengthen the article are here:

- Demand drivers may need to be more detailed as the purchasing of any vaccine and how it is used would influence the strength of each parameter (the high, medium low-ness).
- A few example products and diseases especially in Figure 2 to help illustrate the candidates and why the "scores" are given as such would have greatly helped the reader understand the application of the framework, and increases its usability.
- It is useful to spell out how addressing resistance (AMR) helps the framework, as this is often not well understood. A few example of the fact that reducing usage of antibiotics, lowering infection rates, etc as not all vaccine candidates truly has the potential to reduce AMR, unless a threshold of effectiveness is achieved (that may require some caveats and detail as a next step).
- The authors could also illustrate how single candidates addressing single infections versus combination vaccines (multiple serotypes of a single infectious agent or multiple diseases within a vaccine) will have a different strength to a vaccine portfolio (covering more diseases will definitely outweigh a single disease candidate). Illustrating that could be helpful if space allows.

Apart from that, a very interesting read and well done!

Is the rationale for the Open Letter provided in sufficient detail?
Yes

Does the article adequately reference differing views and opinions?
Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?
Yes
Is the Open Letter written in accessible language?
Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?
Yes

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

**Reviewer Expertise:** Vaccines and the vaccine industry, pharmaceuticals and access to medicine.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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Author Response 01 May 2019

**Bhoomi Lalani,** MSD Wellcome Trust Hilleman Labs, India

Thank you for your detailed and insightful comments. Please see below for responses to your suggestions to strengthen the article.

1. Demand drivers may need to be more detailed as the purchasing of any vaccine and how it is used would influence the strength of each parameter (the high, medium low-ness).
   **Response:** We do agree for a vaccine to be accessible to the end user, procurement and supply chain management is critical. Several global organizations such as UNICEF, PAHO, GAVI, etc. are actively involved in purchasing and distribution of vaccines to low- and middle-income countries. However, as a vaccine R&D organization, first consideration is the need for a vaccine. As time from lab to licensure for a novel vaccine will take ~ 8-10 years, demand dynamics may shift over the years and hence we have considered morbidity/mortality as a measure to assess need rather than actual procurement volumes.

2. A few example products and diseases especially in Figure 2 to help illustrate the candidates and why the “scores” are given as such would have greatly helped the reader understand the application of the framework and increases its usability.
   **Response:** Agree - Figure 2 aims to illustrate why the scores are what they are, by referring to the definitions of high, medium, low in the table. However, since the scores featuring in Figure 2 are weighted average (based on relative importance) and readers are not provided information on weights assigned to individual factors and the calculation of weighted average, direct correlation of scores to definitions is not intuitive. We will revise the table 2 to reflect actual scores along with weighted average.

3. It is useful to spell out how addressing resistance (AMR) helps the framework, as this is often not well understood. A few examples of the fact that reducing usage of antibiotics, lowering infection rates, etc. as not all vaccine candidates truly has the potential to reduce AMR, unless a threshold of effectiveness is achieved (that may require some caveats and detail as a next step).
   **Response:** The article outlines the use of Anti-microbial resistance (AMR), along with additional 2 factors - improving health equity and epidemic potential at the 3rd step for assessing vaccines before including in company portfolio. We will revise the article to elaborate on these factors.

4. The authors could also illustrate how single candidates addressing single infections versus combination vaccines (multiple serotypes of a single infectious agent or multiple diseases within a
vaccine) will have a different strength to a vaccine portfolio (covering more diseases will definitely outweigh a single disease candidate). Illustrating that could be helpful if space allows.

**Response:** Vaccine development is a lengthy process with probability of success ranging from 3%-9% from pre-clinical to licensure for novel candidate. Thus, the probability of success for a combination vaccine will be even lower, and while some companies are simultaneously pursuing development of 2 novel antigens in a combination vaccine; the chances of success will be less than 1%, hence will be a high risk proposition for any organization.

**Competing Interests:** I am the first author of this paper. No other competing interests to disclose.